Haemodynamic response to crystalloids or colloids in shock: an exploratory subgroup analysis of a randomised controlled trial
Nicholas Heming, Souheil Elatrous, Samir Jaber, Anne Sylvie Dumenil, Joel Cousson, Xavier Forceville, Antoine Kimmoun, Jean Louis Trouillet, Jerome Fichet, Nadia Anguel, et al.

To cite this version:
Nicholas Heming, Souheil Elatrous, Samir Jaber, Anne Sylvie Dumenil, Joel Cousson, et al.. Haemodynamic response to crystalloids or colloids in shock: an exploratory subgroup analysis of a randomised controlled trial. BMJ Open, BMJ Publishing Group, In press, 7 (10), pp.e016736. 10.1136/bmjopen-2017-016736. hal-01700757

HAL Id: hal-01700757
https://hal.sorbonne-universite.fr/hal-01700757
Submitted on 5 Feb 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License
BMJ Open

Haemodynamic response to crystalloids or colloids in shock: an exploratory subgroup analysis of a randomised controlled trial

Nicholas Heming,1,2 Souheil Elatrous,3 Samir Jaber,4 Anne Sylvie Dumenil,5 Joël Cousson,6 Xavier Forceville,7 Antoine Kimmoun,8 Jean Louis Trouillet,9 Jérôme Fichet,10 Nadia Anguel,11 Michael Darmon,12 Claude Martin,13 Sylvie Chevret,14 Djillali Annane,1,2 for the CRISTAL Investigators

ABSTRACT

Objective To compare the haemodynamic effect of crystalloids and colloids during acute severe hypovolaemic shock.

Design Exploratory subgroup analysis of a multicentre randomised controlled trial (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill, CRISTAL, ClinicalTrials.gov NCT00318942). Setting CRISTAL was conducted in intensive care units in Europe, North Africa and Canada.

Participants Current analysis included all patients who had a pulmonary artery catheter in place at randomisation. 220 patients (117 received crystalloids vs 103 colloids) underwent pulmonary artery catheterisation.

Intervention Crystalloids versus colloids for fluid resuscitation in hypovolaemic shock.

Outcome measures Haemodynamic data were collected at the time of randomisation and subsequently on days 1, 2, 3, 4, 5, 6 and 7.

Results Median cumulative volume of fluid administered during the first 7 days was higher in the crystalloids group than in the colloids group (3500 (2000–6000) vs 2500 (1000–4000) mL, p=0.01). Patients in the colloids arm exhibited a lower heart rate over time compared with those allocated to the crystalloids arm (p=0.014). There was no significant difference in Cardiac Index (p=0.053), mean blood pressure (p=0.4), arterial lactates (p=0.9) or global Sequential Organ Failure Assessment score (p=0.3) over time between arms.

Conclusions During acute severe hypovolaemic shock, patients monitored by a pulmonary artery catheter achieved broadly similar haemodynamic outcomes, using lower volumes of colloids than crystalloids. The heart rate was lower in the colloids arm.

INTRODUCTION

Fluid resuscitation is a cornerstone of the management of hypovolaemia.1 During hypovolaemic shock, fluids restore intravascular volume, cardiac output, oxygen delivery and reverse peripheral hypoperfusion.2 Resuscitation fluids are divided into two distinct categories, crystalloids and colloids.3 On the one hand, crystalloids dilute the plasma protein content, reducing plasma oncotic pressure which may result in interstitial oedema. The most commonly used crystalloid, isotonic saline, induces hyperchloremic acidosis and acute kidney injury.4–6 On the other hand, colloids are composed of large molecules, increasing their vascular retention and are theoretically more effective for fluid resuscitation.7,8 However, the most commonly used colloid, starch, is associated with acute kidney injury, increased need for renal replacement therapy, accumulation in reticuloendothelial tissues and increased requirements for blood products.9–11 A series of large clinical trials were recently undertaken aimed at determining which fluid was superior for the resuscitation of critically ill patients.12–16

The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial addressed the issue using a pragmatic approach; rather than studying one fluid versus another, both categories of fluids, crystalloids and colloids, were compared in...
severe hypovolaemia. The CRISTAL trial included 2857 subjects treated in 57 intensive care units (ICUs). The primary outcome, 28-day mortality, did not significantly differ, with 25.4% mortality in the colloids arm vs 27% in the crystalloids arm. This finding was similar to results from previous large trials comparing a single colloid to a single crystalloid. However, mortality by 90 days was significantly lower in the colloids arm than in the crystalloids arm (30.7% vs 34.2%). This finding was deemed exploratory. Additionally, the number of days alive at 7 and 28 days without vasopressor therapy was higher in the colloids than in the crystalloids arm. We sought to compare the effect of crystalloids with that of colloids on haemodynamic parameters during hypovolaemic shock. The pulmonary artery catheter (PAC) provides a reliable and reproducible measure of cardiac output as well as the pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP) and derived variables. Therefore, the current study aimed at assessing the haemodynamic effect of crystalloids vs colloids in the CRISTAL participants monitored by PAC.

MATERIALS AND METHODS

Study setting and patients

The current study is a subgroup analysis of a randomised multicentre trial (CRISTAL, ClinicalTrials.gov NCT00318942), comparing the effect of crystalloid vs colloid administration for fluid resuscitation in the ICU on mortality at 28 days. CRISTAL was a non-blinded, pragmatic study. Included subjects were randomised to receive either crystalloids or colloids for hypovolaemia. Crystalloids consisted of isotonic or hypertonic saline as well as buffered solutions, whereas colloids comprised albumin, gelatins, dextrans and hydroxyethyl starches. Patients were managed throughout their ICU stay with the same fluid category. The type of fluid within the assigned group as well as the amount of fluid to be administered was determined by the physician in charge of the patient, the daily total dose of hydroxyethyl starch being restricted to no more than 30 mL/kg of body weight. Physicians could administer albumin in response to demonstrated hypoalbuminaemia. The study protocol was approved by local institutional review boards. Deferred informed consent was obtained from participants or legally authorised surrogates.

For the current ancillary study, among the CRISTAL population, we included all patients who had PAC in place as part of their routine management either prior to or within the first 24 hours of randomisation.

Data collection

Demographic and general characteristics

The following data were prospectively collected at the time of randomisation: age, gender, weight, source of admission, McCabe class and Disability Scale Score. Severity scores included the Glasgow Coma Scale, Simplified Acute Physiology Score II and the Sequential Organ Failure Assessment (SOFA) score. Causes of acute hypovolaemia were stratified in the initial trial as sepsis, trauma or other disorders. We collected a set of symptoms and biological signs of acute hypovolaemia (online supplementary table S1).

Haemodynamic variables

We prospectively measured, for as long as PAC was in place or up to 7 days (whichever occurred first), before randomisation and then once daily (by recording the first value reported in the medical file following the change of shift, ie, typically around 08:00 hours) the following haemodynamic data: heart rate; systolic, diastolic and mean blood pressure; central venous pressure (CVP); systolic, diastolic and mean pulmonary artery pressure; PAOP; Cardiac Index and urinary output. Additionally, mean blood pressure was recorded hourly following the first 24 hours after randomisation. We calculated, using standard formulas, the product of the heart rate and systolic blood pressure (or rate–pressure product (RPP)), a marker of myocardial perfusion requirement, systemic and pulmonary vascular resistances, Stroke Volume Index and Left and Right Ventricular Stroke Work Index. Laboratory values included arterial pH, bicarbonate, lactate and mixed venous oxygen saturation (SvO₂). Finally, to compare colloids with crystalloids in reaching the haemodynamic targets of the 6-hour bundles of the Surviving Sepsis Campaign, we collected these same variables 6 hours after randomisation.

Other variables

We collected before randomisation and daily up to 7 days postrandomisation, the SOFA score and the cumulative volume of administered fluids and throughout the trial the occurrence of the main interventions including packed red cell transfusion and the administration of vasopressors.

Statistical analysis

Quantitative variables are expressed as median (IQR) and categorical variables as number (percentage). The 7-day time course of mean, systolic and diastolic blood pressure, CVP, heart rate, Cardiac Index and daily diuresis as well as the results of arterial blood gases was compared between arms. We then compared systolic, diastolic and mean pulmonary artery pressure and PAOP in both arms. In order to further explore differences between arms, we calculated the RPP as well as the various indexes derived from the use of PAC. Mixed effects models, which are appropriate for clustered and dependent data, were used to study the relationship between treatment arms and the time course of haemodynamic variables as well as the global SOFA score. The area under the curve of mean blood pressure was estimated for each individual, over the first 24 hours, using polynomial integration and compared using the Wilcoxon rank-sum test. Number of days alive without vasopressor therapy was compared using the Wilcoxon rank-sum test. The proportion of
patients reversing signs of hypoperfusion (mean blood pressure (MAP) ≥65 mm Hg, urine output ≥0.5 mL/kg/hour, CVP between 8 and 12 mm Hg and SvO₂ ≥65%, within the first 6 hours of resuscitation) in the sepsis subgroup was compared using the Fisher’s exact test. Complete case analysis was undertaken. Since the current analysis was deemed exploratory and since we report on all statistical analysis done, no correction for multiple testing was deemed necessary. Statistical analyses were performed using SAS V.9.3 (SAS) and R V.2.13.0 (http://www.R-project.org/) software. Tests were two sided. A value of p<0.05 was considered significant.

RESULTS

Patients

Among the CRISTAL population, 220 subjects had PAC in place as part of their routine management, of which 103 received colloids and 117 crystalloids, accounting for a total of 645 catheter-days. PAC was generally in place around the time of randomisation, either before (n=79; 36%) or within 24 hours post-randomisation (n=84; 38%). Characteristics of the subgroup of PAC-monitored patients were similar to those of the whole population of the CRISTAL study, regarding age, gender and initial severity scores (table 1). Haemodynamic variables at the time of randomisation are described in table 2.

Treatment effects on haemodynamic variables

Median cumulative volume of fluid administered during the first 7 days in the ICU was higher in the crystalloids than in the colloids arm (3500 (2000–6000) vs 2500 (1000–4000) mL, respectively (p=0.01). The distribution of fluid types within each study arm is displayed in online supplementary table S2. During the first 24 hours following randomisation, mean blood pressure did not

| Table 1 Main characteristics at baseline according to randomisation arm |
|----------------------|------------------|------------------|------------------|------------------|
|                      | All patients n=220 | Colloids arm n=103 | Crystalloids arm n=117 | p Value |
| Age, median (IQR), years | 68 (57–77) | 69 (59–79) | 67 (52–75) | 0.05 |
| Male sex, no (%) | 141 (64.1) | 71 (68.9) | 70 (59.8) | 0.20 |
| Weight, median (IQR), kg | 72 (63–85) | 71.3 (62.3–84.5) | 73.4 (64–88) | 0.49 |
| Reason for ICU admission, no (%) | 148 (67.3) | 70 (68) | 78 (66.7) | 0.58 |
| Medical | 41 (18.6) | 20 (19.4) | 21 (17.9) | 0.58 |
| Scheduled surgery | 29 (13.2) | 12 (11.7) | 17 (14.5) | 0.58 |
| Emergency surgery | 2 (0.9) | 1 (1) | 1 (0.9) | 0.93 |
| Non-surgical trauma | 104 (47.3) | 39 (37.9) | 65 (55.6) | 0.11 |
| Hospital ward | 102 (46.4) | 56 (54.4) | 46 (39.3) | 0.11 |
| Other ICU | 11 (5) | 7 (6.8) | 4 (3.4) | 0.58 |
| Long-term care facility | 1 (1.3) | 1 (0.9) | 1 (0.9) | 0.58 |
| McCabe class, no (%) | | | | |
| No underlying disease or no fatal disease | 129 (58.6) | 62 (60.2) | 67 (57.3) | 0.83 |
| Underlying ultimately fatal disease (>5 years) | 83 (37.7) | 38 (36.9) | 45 (38.5) | 0.83 |
| Underlying rapidly fatal disease (<1 year) | 8 (3.6) | 3 (2.9) | 5 (4.3) | 0.83 |
| Knaus Disability Scale, no (%) | | | | |
| A | 35 (15.9) | 15 (14.6) | 20 (17.1) | 0.28 |
| B | 82 (37.3) | 33 (32) | 49 (41.9) | 0.28 |
| C | 64 (29.1) | 33 (32) | 31 (26.5) | 0.28 |
| D | 37 (16.8) | 20 (19.4) | 17 (14.5) | 0.28 |
| Glasgow Coma Scale, median (IQR) | 11 (3–15) | 13 (3–15) | 11 (3–15) | 0.61 |
| SAPS II, median (IQR) | 50 (33–65) | 51 (36–66) | 50 (30–64) | 0.41 |
| SOFA, median (IQR) | 8 (5–11) | 8 (5–11) | 9 (5–12) | 0.80 |
| Sepsis, no (%) | 108 (49.1) | 52 (50.5) | 56 (47.9) | 0.79 |

Knaus Scale A. prior good health and no functional limitations; B. mild to moderate limitation of activity owing to chronic medical problem; C. chronic disease producing serious but not incapacitating restriction of activity; D. severe restriction of activity due to disease; includes persons bedridden or institutionalised due to illness.

ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.
Open Access

significantly differ between treatment arm (mean area under the curve 78 (68–84) for colloids vs 77 (70–84) mm Hg/hour for crystalloids (p=0.6)). The heart rate was lower in the colloids than in the crystalloids group (p=0.014) (figure 1). Systolic, diastolic and mean blood pressure did not significantly differ between arms (p=0.6, p=0.2 and p=0.4, respectively) (online supplementary figure S1-S3). Cardiac Index, although the difference was not statistically significant (p=0.053), was higher in patients treated with colloids compared with those treated with crystalloids (figure 2). CVP did not differ between both arms (p=0.3) (online supplementary figure S4). Subjects in the colloids arm exhibited a lower RPP (p=0.036) (figure 3). Arterial pH, arterial levels of bicarbonate and lactate did not differ between groups (p=0.3, p=0.3 and p=0.9, respectively) (online supplementary figure S5-S7). SvO₂, daily urine output (online supplementary figure S8) and the SOFA score did not differ between both arms (p=0.9, p=0.15 and p=0.3, respectively). Haemodynamic stability was reached through a similar use of vasopressors and a similar use of blood transfusion (table 3). Other relevant outcomes did not significantly differ between both groups. No serious adverse event related to PAC placement was reported during the trial.

| Table 2 | Physiological values at baseline according to randomisation |
|-----------------|-----------------|-----------------|-----------------|
|                | All patients    | Colloids arm    | Crystalloids arm |
|                | n=220           | n=103           | n=117           | p Value |
| Heart rate, median (IQR), beats/min (n=218) | 100 (89–120) | 99 (88–115) | 103.5 (90–124) | 0.25 |
| Systolic blood pressure, median (IQR), mm Hg (n=219) | 92 (76–109) | 92.5 (73–108) | 91 (80–111) | 0.89 |
| Diastolic blood pressure, median (IQR), mm Hg (n=181) | 48 (40–58) | 47 (37–57) | 50 (41–58) | 0.19 |
| Mean blood pressure, median (IQR), mm Hg (n=184) | 66 (56–77) | 64.5 (53–75) | 67 (60–78) | 0.21 |
| Central venous pressure, median (IQR), mm Hg (n=81) | 9 (7–12) | 10 (6–12) | 9 (7–13) | 0.96 |
| Pulmonary artery systolic pressure, median (IQR), mm Hg (n=64) | 32 (27–39) | 32 (25–40) | 32 (27–38) | 0.59 |
| Pulmonary artery diastolic pressure, median (IQR), mm Hg (n=64) | 17 (14–22) | 16 (12–21) | 18 (15–22) | 0.24 |
| Pulmonary artery mean pressure, median (IQR), mm Hg (n=78) | 22 (17–28) | 21 (17–28) | 23 (19–28) | 0.51 |
| Pulmonary artery occlusion pressure, median (IQR), mm Hg (n=53) | 12 (8–15) | 12 (7–15) | 12 (9–16) | 0.30 |
| Cardiac Index, median (IQR), L/min/m² (n=75) | 2.5 (2–3.1) | 2.4 (2.2–3) | 2.5 (2–3.3) | 0.94 |
| Systemic vascular resistance, median (IQR), (dyn s/cm⁵) (n=49) | 893 (690–1208) | 906 (699–1146) | 830 (637–1238) | 0.40 |
| Pulmonary vascular resistance, median (IQR), (dyn s/cm⁵) (n=33) | 170 (121–260) | 172 (135–343) | 0.35 (120–230) | |
| Stroke Volume Index, median (IQR), mL/m² (n=74) | 26 (21–34) | 27 (22–34) | 24 (20–33) | 0.40 |
| Left-Ventricular Stroke Work Index, median (IQR), (g m)/m² (n=38) | 20 (14–31) | 20 (14–33) | 17 (14–29) | 0.73 |
| Right-Ventricular Stroke Work Index, median (IQR), (g m)/m² (n=52) | 5 (2–6) | 4 (2–5) | 5 (3–8) | 0.12 |
| pH, median (IQR) (n=196) | 7.34 (7.26–7.41) | 7.36 (7.28–7.43) | 7.33 (7.22–7.40) | 0.038 |
| HCO₃⁻, median (IQR), mmol/L (n=110) | 20.8 (17.6–24.2) | 21.3 (17–24.6) | 20 (18–23.6) | 0.44 |
| Lactate, median (IQR), mmol/L (n=155) | 2.3 (1.3–4.9) | 2.3 (1.3–4.6) | 2.25 (1.4–5) | 0.94 |
| SvO₂, median (IQR), % (n=33) | 71 (58–80) | 63 (58–73) | 74 (57–81) | 0.31 |

SvO₂, mixed venous oxygen saturation.
Sepsis subgroup
Among PAC-monitored patients, 108 subjects were stratified in the sepsis group, of which 52 were allocated to colloids and 56 to crystalloids. We compared the number of patients achieving mean blood pressure levels ≥65 mm Hg and urine output ≥0.5 mL/kg/hour within the first 6 hours. A total of 35/51 (69%) patients in the crystalloids arm achieved MAP ≥65 mm Hg after 6 hours vs 31/47 (66%) in the colloids arm (p=0.8); 25/38 (66%) patients in the crystalloids arm achieved urine output ≥0.5 mL/kg/hour after 6 hours vs 17/28 (61%) in the colloids arm (p=0.8). Limited data precluded the analysis of CVP and SvO₂ values during the first 6 hours following randomisation.

DISCUSSION
We found that colloids achieved broadly similar resuscitation goals to crystalloids using lower volumes of administered fluids. Additionally, colloids may exhibit a favourable impact on heart rate and RPP. Colloids did not affect any other haemodynamic endpoints. We found, in patients with sepsis, no evidence for a superiority of colloids over crystalloids in achieving haemodynamic targets of the 6-hour bundle of the Surviving Sepsis Campaign. The fact that the mean arterial blood pressure and Cardiac Index did not significantly differ in both groups may be explained by the fact that physicians sought to achieve similar targets in both groups, whether by the administration of fluids, packed red cell or vasopressors.

Tachycardia may increase myocardial work, with subsequent excessive myocardial energy expenditure, and may be associated with worse outcomes through excessive cardiovascular morbimortality. Myocardial protection is of particular interest in the ageing population currently common in most ICUs, since it may somewhat relieve cardiovascular mortality.

Table 3  Study outcome and blood transfusion by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Colloids arm (n=103)</th>
<th>Crystalloids arm (n=117)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days alive without, median (IQR)</td>
<td>18 (0–25)</td>
<td>20 (0–24)</td>
<td>0.98</td>
</tr>
<tr>
<td>Vasopressor therapy within the first 28 days</td>
<td>2 (2–3)</td>
<td>2 (2–4)</td>
<td>0.59</td>
</tr>
<tr>
<td>Units of packed red cell transfused, median (IQR)</td>
<td>2 (2–3)</td>
<td>2 (2–4)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
The efficacy of fluid resuscitation is determined by the 
capacity of administered fluids to remain in the intravas-
cular space. The superior oncotic pressure of colloids is 
associated with increased intravascular expansion capacity 
compared with crystalloids. In order to achieve similar 
resuscitation goals, compared with colloids, between 20% 
and 50% more volume of crystalloids should be adminis-
tered. Inflammatory states such as those observed 
during critical illness are usually associated with endothe-
lial dysfunction, leading to interstitial oedema. Reducing 
volumes of administered fluids may be of clinical benefit, 
and a negative fluid balance improved outcome in Acute 
Respiratory Distress Syndrome, a frequent complication 
of sepsis. In septic shock, a positive fluid balance has been 
associated with a worse outcome. However, short-term haemodynamic benefits of fluids may in some 
cases be offset by long-term deleterious consequences. 
Indeed, some types of colloids may be unsafe. Starches, 
the most commonly used colloid, may be associated with 
increased risk of acute kidney injury and increased need 
for renal replacement therapy, both in the general ICU 
population and in sepsis. The daily total volume of 
hydroxyethyl starch which could not exceed 30 mL/kg in 
the CRISTAL trial led patients having exceeded that limit 
to subsequently receive albumin or crystalloids. The use 
of starches has now been restricted in the ICU in Europe 
and the USA. The implication is that from a haemo-
dynamic point of view, fluid resuscitation with colloids 
or crystalloids is broadly equivalent—maybe with a slight 
advantage for colloids—although the price of resuscita-
tion using crystalloids would be an increase in the total 
volume of administered fluids.

Our findings are similar to those of several of the other 
major fluid trials. Most trials compared one type of colloid 
with one type of crystalloid. The Saline versus Albumin 
Fluid Evaluation (SAFE) study assessed 4% albumin or 
9% saline in critically ill patients. Albumin admin-
istration was associated with a statistically significant 
lower heart rate on the first day of treatment, although 
the difference was small. The Albumin Italian Outcome 
Sepsis (ALBIOS) study compared 20% albumin (titrated 
to achieve a serum albumin concentration of over 30 g/L) 
to 9% saline in patients suffering from severe sepsis. 
Over the first 7 days after randomisation, patients in the 
albumin arm experienced lower heart rate and a shorter 
duration of vasopressor therapy. The Crystalloid versus 
Hydroxyethyl Starch Trial (CHEST) trial randomised 
critically ill patients to receive hydroxyethyl starches or 
9% saline. Among the various haemodynamic targets, 
higher CVP over the first 4 days following randomisation 
was the only statistically significant difference between 
hydroxyethyl starches and 9% saline-treated patients. The 
authors of the CHEST study concluded that crystal-
loids were as effective as colloids for initial resuscita-
tion. The Scandinavian Starch for Severe Sepsis/Septic 
Shock (6S) trial allocated either hydroxyethyl starches or 
Ringer’s acetate to severe sepsis patients. The haemo-
dynamic targets were similar between both arms over 
the first 24 hours after randomisation. Of note, subjects 
enrolled in both CHEST and 6S studies were enrolled up 
to 24 hours after their admission to the ICU, hence after 
The initial resuscitation phase. However, in CRISTAL, 
patients were randomised and treated as early as possible 
after the occurrence of shock. Patients in CRISTAL were 
treated by a variety of colloids including starches, but also 
gelatins, in approximately one-third of patients. Gelatins 
have been less extensively studied in large clinical trials, 
and their drawbacks are not as well characterised. Their 
use may have somewhat offset any deleterious effect 
related to starches when administered in the colloid 
group. Overall, these findings should help expand our 
knowledge pertaining to the field of fluid resuscitation.

Our study has some limitations. First, our subgroup 
accounts for less than 10% of the global CRISTAL trial 
population; the small size of our subgroup is related to a 
steady decline in the use of the PAC during the CRISTAL 
trial, amidst reports that the use of PAC does not alter 
outcome in ICU patients and increased availability of 
less invasive haemodynamic monitoring tools. Moreover, 
some selection bias may have been introduced, owing to 
the fact that PA catheterisation was not performed within 
24 hours of randomisation in about one-fourth of the sample. Complete case analyses performed on available 
measurements further assume that missing mechanisms 
were unrelated to patient status. Finally, some inflation 
of type I error rate associated with the number of tests 
undertaken is possible, meaning that interpretation of 
results should be exploratory.

**CONCLUSION**

CRISTAL participants monitored by a PAC reached 
broadly similar haemodynamic outcomes whether treated 
by crystalloids or by colloids. Colloids were associated 
with lower heart rates and lower volume of administered 
fluids than crystalloids.

**Author affiliations**

1. General Intensive Care Unit, Raymond Poincaré Hospital, Garches, France
2. U1173 Lab Inflammation & Infection, University of Versailles, Saint-Quentin-en-Yvelines - INSERM, Garches, France
3. Service de réanimation, Centre Hospitalo-Universitaire Tahar Sfar, University of Monastir, Mahdia, Tunisia
4. Saint-Eloi University Hospital, Montpellier, France
5. Antoibe Béclère Hospital, Clamart, France
6. Reims University Hospital, Robert Debré Hospital, Reims, France
7. General Hospital, Meaux, France
8. Intensive Care Unit Brabois, Heart and Vessels Institute, Nancy University Hospital, Nancy, France
9. Pitie Salpêtrière Hospital, Paris, France
10. Centre Cardiologique du Nord, Saint-Denis, France
11. Bicêtre Hospital, Le Kremlin-Bicêtre, France
12. Saint Louis Hospital, Paris, France
13. AP-HM Hôpital Nord, Marseille, France
14. Biostatistic Team, Saint Louis Hospital, Paris, France

**Acknowledgements** We thank all the investigators and patients of the CRISTAL trial. We would like to thank Cendrine Chauffaut of the Biostatistic Team, Saint Louis Hospital for her technical assistance.
Contributors NH, SC and DA were involved in study concept and design. NH, SE, SJ, ASD, JC, XF, AK, JLT, JF, NA, MD and CM acquired the data; SC was involved in statistical analysis; NH, SC and DA were involved in analysis and interpretation of data; NH and DA drafted the manuscript; all authors critically revised the manuscript for important intellectual content; DA was involved in study supervision; all authors read and approved the final manuscript.

Funding The CRISTAL study was funded by 2001 and 2010 grants (AOM 01 020) from the French Ministry of Health.

Competing interests None declared.

Ethics approval Committee for the Protection of People of Saint-Germain-en-Laye for French sites and at institutional review boards elsewhere.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Individual data are available by contacting DA at djilali.annane@aphp.fr.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

11. Schetz M, Shaw AD, Vincent J-L. Is the literature inconclusive about the harm of HES? We are not sure. Intensive Care Med 2012;120.
Haemodynamic response to crystalloids or colloids in shock: an exploratory subgroup analysis of a randomised controlled trial

Nicholas Heming, Souheil Elatrous, Samir Jaber, Anne Sylvie Dumenil, Joël Cousson, Xavier Forceville, Antoine Kimmoun, Jean Louis Trouillet, Jérôme Fichet, Nadia Anguel, Michael Darmon, Claude Martin, Sylvie Chevret and Djillali Annane

BMJ Open 2017 7: 
doi: 10.1136/bmjopen-2017-016736

Updated information and services can be found at: 
http://bmjopen.bmj.com/content/7/10/e016736

These include:

References
This article cites 28 articles, 0 of which you can access for free at: 
http://bmjopen.bmj.com/content/7/10/e016736#ref-list-1

Open Access
This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Intensive care (215)

Notes

To request permissions go to: 
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to: 
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to: 
http://group.bmj.com/subscribe/