Accepted January 2014

EDITORIAL

Comment on CRISTAL study

L. Zafrani, C. Ince

Department of Intensive Care, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Correspondence

C. Ince – e-mail: c.ince@amc.uva.nl

Keyword – **CRISTAL study**

In the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) study, Annane and co-authors compared patients receiving crystalloids (n=1443) with those receiving colloids (n=1414) for acute hypovolemic shock in 57 intensive care units (ICU) in France, Belgium, North Africa, and Canada.[1] Randomization was stratified by centre and by diagnosis (i.e. sepsis, multiple trauma and other causes of hypovolemic shock). Therapy in the trial was open label but outcome assessment was blinded to treatment assignment. For each patient the choice for either use of crystalloid or colloid was determined by randomization but the type of colloid or crystalloid used was left to the discretion of the clinician. In this design, in the crystalloid group the type of solution used was 86% isotonic saline, 18% Ringer's lactate and 4% hypertonic saline; in the colloid group, 69% hydroxyethylstarch (HES), 6% albumin 4%, and 14% albumin 12%. Patients treated with colloids received less fluid than those treated with crystalloids. Mortality did not differ at day 28. However, patients treated with colloids had more days free of vasopressor therapy and mechanical ventilation at day 7 and day 28 and had a lower mortality at 90 days (30.7% in the colloids group versus 34.2% in the crystalloids group). No differences in the incidence of organ failure or renal replacement therapy were detected between the two groups.[1]

The choice of fluid resuscitation for patients in hypovolemic shock remains a highly controversial issue. In the Saline Versus Albumin Fluid Evaluation (SAFE) study, which included 6997 ICU patients, Finfer et al. did not find any difference in terms of outcomes at 28 days between patients resuscitated with either albumin 4% or normal saline.[2] In 2008, in the VISEP trial (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis), Brunkhorst et al. randomly assigned 537 patients with severe sepsis to receive either 10% pentastarch (200kD) or Ringer's lactate for fluid resuscitation and found that starch was harmful, worsening renal outcomes and possibly increasing mortality.[3] The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) study that included 804 patients with severe sepsis, found that 130kD HES increased 90-day mortality and worsened acute kidney injury.[4] The Crystalloid versus Hydroxyethyl (CHEST) trial reported a higher incidence of renal replacement therapy with HES compared to saline.[5] In a recent study published in *Critical Care* in 2013, Meybohm et al. re-evaluated prospective randomized controlled trials that compared the effect of colloids with crystalloids in critically ill patients.[6] They defined 6 major criteria needed for a trial to be taken into consideration providing valid evidence for the comparison between different fluid types. They proposed a 6-points score including short time interval from shock to randomization (<6 h), restricted use for initial volume resuscitation, use of any consistent algorithm for haemodynamic stabilization, reproducible indicators of hypovolemia, maximum dose of HES, and exclusion of patients with pre-existing renal failure or renal replacement therapy. If this score is applied to the CRISTAL study it scores a total of 5 points, whereas the VISEP, 6S and CHEST trial score respectively 2, 1 and 2 points.

The design of the CRISTAL trial is of particular interest for many reasons. First, patients had received no prior fluids for resuscitation during their ICU stay which may have been a considerable bias in many previous studies.[3,4] In the CHEST and 6S trials, patients had already been resuscitated, were normotensive and arguably were not in need of the administered fluid regimens for the purpose of resuscitation. In this context one can question whether testing the effects of crystalloids to colloids in a blinded fashion is an appropriate study design. From this point of view, the CRISTAL is clinically more significant since it tests the efficacy in a clinical setting where fluids are indeed needed for resuscitation in a state of hypovolemia. Second, acute hypovolemia was confirmed at inclusion by hemodynamic parameters measurements (i.e. the combination of hypotension with evidence for low

filling pressures and low cardiac index as assessed either invasively or noninvasively and, signs of tissue hypoperfusion or hypoxia), assessing that these patients really needed fluid resuscitation. Indeed, adequate evidence of hypovolemia is of utmost importance in order to interpret data concerning the administration of colloids or crystalloids and may have been lacking previously.[4] Third, the total dose of starches in the trial by Annane et al. never exceeded the dose recommended by regulatory agencies and they excluded patients with severe chronic renal failure, making the use of colloids (especially HES) safer. Indeed, in the CRISTAL trial, contrary to contemporary opinion on the effects of HES products based on the CHEST and 6S trial the use of these starches in the CRISTAL trial was not associated with renal dysfunction.

How can we integrate Annane et al.'s study into physiological data? From a physiological point of view, acute volume resuscitation with colloids should result in less amounts of fluids needed for hemodynamic stabilization compared to crystalloids.[7] Moreover, one of the unwanted effects of fluids is the hemodilution-induced reduction of the oxygen carrying capacity of blood.[8] In this regard, hematocrit would have been an easy an interesting parameter to look at. In a recent study, Konrad et al. compared in pigs the renal microvascular oxygenation effects by using either a crystalloid solution or an HES for acute normovolemic hemodilution to a fixed hematocrit of 15%.[9] In their model, they found that more harm was inflicted on the kidney by the use of crystalloids than HES. In the future, we can expect that microcirculation measurements in humans may help to guide fluid resuscitation.

In contrast, colloid-induced acute kidney injury, with morphological lesions of the proximal tubular cells, or osmotic nephrosis has been reported after the infusion of low-molecular-weight dextran or HES, especially with the first generation products. The tubular lesions reflect the accumulation of proximal tubular lysosomes due to pinocytosis of exogenous osmotic solutes, for example, mannitol, sucrose, iodinated contrast media, or colloids[10] So how can we combine these contradictory data? First of all, if colloids are used, it is extremely important to use a colloid of any kind with due care, following recommended doses, as Annane and co-authors did in their study. HES should not be given to ICU patients for long periods of time with high cumulative doses. Second, third-generation iso-oncotic products appear to be safer when used correctly and should be preferred in the next clinical trials. If physiology cannot be a substitute for clinical data, a physiological approach is useful for addressing the issue because it can focus on mechanisms and deliver clarity regarding the disputed issues and provide guidance for the design of appropriate clinical trials.[11]

As well as the major contribution of the results from the Annane et al. study, important caveats remain in the CRISTAL study. First, different types of colloids and crystalloids have been mixed in each group and side-effects can be different from one molecule to another. As mentioned above and due to potential harmful effects (especially to the kidneys) of hyperoncotic colloids, these should be ideally avoided. Second, as pointed out by authors, the differences in 90-day mortality rates between the two groups should be interpreted with caution. Indeed, 90-day mortality was a secondary outcome and the confidence intervals approach 1. Finally, if we go back to the 6-point score suggested by Meybohm et al.,[6] the CRISTAL study, as many other previous studies, lacks a standardized protocol and algorithm with predefined hemodynamic targets for fluid resuscitation and sequential reassessment of volume status after colloids or crystalloids have been administered.

In conclusion, the debate concerning colloids and crystalloids has not been yet settled. The CRISTAL study adds a new milestone to the issue of fluid resuscitation but also raises new questions that will need to be answered in the next few years with appropriate and well-designed prospective studies.

References

1. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809-17.
2. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247-56.
3. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125-39.
4. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124-34.
5. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901-11.
6. Meybohm P, Aken HV, Gasperi AD, et al. Re-evaluating currently available data and suggestions for planning randomised controlled studies regarding the use of hydroxyethyl starch in critically ill patients – a multidisciplinary statement. Crit Care. 2013;17:R166.
7. Jacob M, Chappell D, Hofmann-Kiefer K, et al. The intravascular volume effect of Ringer's lactate is below 20%: a prospective study in humans. Crit Care 2012;16:R86.
8. Legrand M, Mik EG, Balestra GM, et al. Fluid resuscitation does not improve renal oxygenation during hemorrhagic shock in rats. Anesthesiology. 2010;112:119-27.
9. Konrad FM, Mik EG, Bodmer SI, et al. Acute normovolemic hemodilution in the pig is associated with renal tissue edema, impaired renal microvascular oxygenation, and functional loss. Anesthesiology. 2013;119:256-69.
10. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis. 2008;51:491-503.
11. Ince C. The great fluid debate: when will physiology prevail? Anesthesiology. 2013;119:248-9.