Fluid resuscitation 'post Boldt': throwing out the baby with the bathwater?

The retraction of many papers authored by Professor Joachim Boldt has refocused attention on the longstanding crystalloid–colloid debate. On 28 October 2010 Professor Steven Shafer, editor of *Anesthesia and Analgesia*, published the first in a series of retractions of papers of which Professor Boldt is an author (Shafer, 2010).

Initial concerns expressed to *Anesthesia and Analgesia* centred around the implausibly low variability on some cytokine assays reported in a paper comparing human albumin solution with a semi-synthetic colloid (hydroxyethyl starch) as cardiopulmonary bypass priming solutions (Boldt et al, 2009). Investigations by the Rheinland-Pfalz State Medical Board were unable to find any evidence of ethical committee approval, written informed consent, randomization process or follow-up questionnaires for the study, all of which were described in the original manuscript. Consequently, this paper was retracted on the basis that it was fraudulent (Shafer, 2011).

Further enquiries by the same medical board identified another 88 published manuscripts since 1999 for which they were unable to verify ethical committee approval where it was required. This culminated in a statement by the editors-in-chief of 16 journals, including all the major anaesthesia journals, on 4 March 2011, stating that all 88 papers would be retracted on the basis that the research was unethical (in accordance with the Declaration of Helsinki) (Rasmussen et al, 2011). The proportion of these that are also fraudulent is uncertain.

Uncertainty also hangs over a large number of papers published before 1999 when Professor Boldt worked at a different institution. This has important implications for research governance and journal editorial policy, but there may also be significant implications for clinical practice if more of these papers are fraudulent. So how do we assess the impact of these changes on current practice? Is there still a place for colloid administration in the light of these findings or is the colloid–crystalloid controversy finally moving towards a conclusion?

Crystalloids *vs* colloids

The use of intravenous fluids can be divided into administration for maintenance and resuscitation. While there remains controversy over which crystalloid solution to use, there is a settled consensus that crystalloids, and not colloids, are the appropriate maintenance fluids.

In the choice of resuscitation fluid, the controversy between crystalloids and colloids flourishes. The theoretical benefits of colloids over crystalloids centre on the greater plasma volume expansion per unit volume infused, and the consequent reduction in extravascular fluid accumulation and oedema formation. Empirical data confirm that, while this general principle is true, the difference is smaller than the 1:3 to 1:5 ratio predicted theoretically.

Three large blinded clinical trials in which patients were randomized to colloid or crystalloid fluids for resuscitation demonstrated overall colloid:crystalloid volume ratios between 1:1.3 and 1:1.6 (Finfer et al, 2004; Wills et al, 2005; Brunkhorst et al, 2008). For the newer, lower molecular weight starches, this ratio may be nearer 1:1.6 to 1:2.0 (Hartog et al, 2011).

Additional beneficial effects on endothelial function, the inflammatory cascade and microcirculatory function have been shown in animals but their relevance in humans is uncertain (Grocott et al, 2005). These putative benefits must be balanced against adverse effects. There is evidence of renal dysfunction and coagulopathy, particularly with higher doses of hydroxyethyl starch solutions, and of increased rates of adverse drug reactions including anaphylaxis and itching (Grocott et al, 2005).

A full evaluation of the impact on clinical practice of research malpractice in relation to Professor Boldt's publications cannot be made until the status of each individual paper is clarified. In the mean time, some comments can be made based on the evidence as it stands today.

There are specific clinical circumstances where colloid administration is integral to an intervention that is known to be beneficial. For example, goal-directed fluid therapy in elective major surgery involves synthetic colloid fluid challenges guided by blood flow measurements, or the use of human albumin solution in plasma exchange techniques (McLeod, 2006; Mowatt et al, 2009). Perioperative crystalloid overload is recognized to be harmful (although 'restrictive' and 'liberal' labels are unhelpful and misleading) and colloid therapy has a role in avoiding this (Brandstrup et al, 2003; Grocott et al, 2005; Chappell et al, 2008). The general case for the use of colloids for resuscitation of hypovolaemia is more complex. Characterization of the colloid–crystalloid debate as one between Europe and the USA is simplistic; although indications for colloids and crystalloids vary from hospital to hospital, both are used in most institutions on either side of the Atlantic.

The Cochrane Collaboration promptly updated the relevant systematic reviews to incorporate additional analyses based on the 'worst case' assumption: that all papers by Boldt and collaborators may be withdrawn. Overall, the results of these reviews are unaltered. The results of 'Colloids *vs* crystalloids for fluid resuscitation in the critically ill' review are unchanged, so the conclusion stands: 'There is no evidence from RCTs [randomized controlled trials] that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery' (Perel and Roberts, 2011).

The point estimate of effect for one comparison within 'Colloid solutions for fluid resuscitation' is altered by exclusion of papers by Boldt and colleagues (albumin or plasma protein fraction *vs* hydroxyethyl starch: pooled relative risk changed from 1.14 (95% confidence interval 0.91–1.43) to 0.97 (95% confidence interval 0.70–1.35)) but this does not alter the overall conclusion: 'there is no evidence that one colloid solution is more effective or safe than any other, although the confidence intervals are wide and do not exclude clinically significant differences between colloids' (Bunn et al, 2011). A third systematic review of

'Intravenous fluids for aortic aneurysm surgery' included no Boldt manuscripts and concluded 'no single fluid affects any outcome measure significantly more than another fluid across a range of outcomes' (Toomtong and Suksompong, 2010).

These, perhaps surprising, results occur because Professor Boldt's numerous papers tended to describe small studies with few deaths. Systematic reviews in this area have a number of limitations: heterogeneity of included colloid types, heterogeneity of indications for use, and inclusion of studies conducted over several decades on a background of changing practice and outcomes.

Two large randomized controlled trials in critical care provide useful data (Finfer et al, 2004; Brunkhorst et al, 2008). Neither found any difference in mortality, incidence of organ failure, or length of hospital or intensive care stay between patients receiving crystalloid and colloid fluid resuscitation. Any argument that either hydroxyethyl starch or human albumin solution are clearly harmful is thus difficult to sustain; these data suggest that any harmful effects are balanced by beneficial ones and raise the likelihood that while some patients may be at risk from colloid solutions (e.g. those with pre-existing renal dysfunction), others may benefit.

Consistent with this, sub-group analyses from the SAFE study (blinded human albumin solution given to unselected critically ill patients) showed that human albumin solution increased mortality in patients with traumatic brain injury, but may be of benefit in severe sepsis which showed a trend towards reduced mortality (Finfer et al, 2004).

In a study examining the efficacy of volume substitution and insulin therapy (VISEP), patients with severe sepsis or septic shock exhibited hydroxyethyl starch dose-dependent increases in acute renal failure and 90-day mortality (Brunkhorst et al, 2008). However, patients in the hydroxyethyl starch group received a median cumulative dose of 70.4 ml/kg (equivalent to 4.5–6 litres of hydroxyethyl starch) and there was no hint of a mortality difference below 40 ml/kg. Avoidance of extreme high doses of colloids is clearly wise, but the same could be said of almost any intervention.

Conclusions

The literature is consistent with either colloids or crystalloids being beneficial or harmful relative to the other and does not allow us to distinguish satisfactorily between the relative benefits or harms of individual colloids. However, it identifies sub-groups of patients in whom colloids are harmful, beneficial or likely to be beneficial.

Calls to withdraw colloids based on current events are neither rational, based on current clinical evidence, nor consistent with approaches to other interventions. To quote from a post-Boldt editorial in *Anesthesia and Analgesia*, a journal likely to tend to a conservative approach in this area: 'For those whose clinical practice is strongly influenced by the available evidence, the approach to fluid therapy in hypovolemia is likely to remain largely unchanged…' (Reinhart and Takala, 2011). High quality clinical trials are clearly needed, and several are currently underway. We will have a clearer picture soon, but in the mean time we should base our decisions on the available clinical literature and avoid inappropriate excess colloid administration. Rumours of the death of colloids are greatly exaggerated. BJHM

MPW Grocott
Consultant in Critical Care Medicine
Southampton University Hospitals NHS Trust
Southampton SO16 6YD
Honorary Reader
University of Southampton
TJ Gan
Professor of Anesthesiology
Vice Chairman of Clinical Research
Duke University Medical Center, Durham
North Carolina, USA

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KEY POINTS

- The retraction of multiple papers authored by Professor Joachim Boldt (because of lack of ethical approval or fraud) has refocused attention on the longstanding crystalloid–colloid debate.
- These events have important implications for research governance and journal editorial policy. However, the implications for clinical practice are less significant than might be expected, because of the small size and low mortality of many of the Boldt studies.
- Published literature is consistent with either colloids or crystalloids being beneficial or harmful relative to the other and does not allow us to distinguish satisfactorily between the relative benefits or harms of individual colloids.