

The appropriate role of colloids in managing fluid imbalance: a critical review of recent meta-analytic findings

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Abstract

Three meta-analyses have recently been reported on the relationship between choice of resuscitation fluid and risk of mortality in critically ill patients. The relative risk of death (1.16–1.19) in two of the meta-analyses was slightly higher in colloid than crystalloid recipients; however, this observation was not statistically significant. In the third meta-analysis, 6% (95% confidence interval [CI], 3–9%) pooled excess mortality was documented in patients receiving albumin for hypovolaemia, burns or hypoalbuminaemia. The mortality difference in hypovolaemia patients (4%; 95% CI, 0–8%) was not statistically significant. A variety of serious limitations apply to the three meta-analyses, suggesting that their findings be interpreted cautiously. More than one-half of the randomized controlled trials (RCTs) included in the meta-analyses were reported prior to 1990 and hence do not reflect current practice. Each meta-analysis included only a subset of relevant RCTs, and therefore the scope of inferences to be drawn from the meta-analytic results is limited. The meta-analyses combined RCTs that were notably heterogeneous with respect to patient characteristics, type of illness, administered fluids and physiologic endpoints. Differences in illness severity, concomitant therapies and fluid management approaches were not taken into account. Very few of the RCTs were blinded. The meta-analyses do not support the conclusion that choice of resuscitation fluid is a major determinant of mortality in critically ill patients, nor do they support changes to current fluid management practice. Changes such as exclusive reliance on crystalloids would necessitate a reassessment of the goals and methods of fluid therapy. Since the effect on mortality may be minimal or non-existent, choice of resuscitation fluid should rest on whether the particular fluid permits the intensive care unit to provide better patient care.

Keywords: colloids, hetastarch, meta-analysis, mortality, serum albumin

Introduction

The recent publication of three meta-analyses [1–3] has intensified the long-standing debate regarding the merits of colloids to expand the plasma space in critically ill patients. Two of these meta-analyses concluded that

excess mortality was associated with the use of colloids generally [1] and of albumin specifically [2], and proposed that such use be curtailed outside the context of RCTs. The third meta-analysis concluded there was no overall mortality difference associated with colloid versus crystalloid resuscitation [3]. Furthermore, due to methodologic

limitations, evidence-based clinical recommendations were not deemed to be warranted on the basis of the meta-analysis [3].

Critical care physicians must now assess what impact, if any, these meta-analyses should exert upon current clinical practice. This assessment needs to include a close and rigorous examination of the meta-analyses and the RCTs underlying them.

Colloid meta-analyses

The systematic review by Schierhout and Roberts [1] identified 26 RCTs [4–29] encompassing 1622 patients receiving colloid or crystalloid. Mortality was adopted as the main outcome measure in the meta-analysis of these RCTs. Mortality among patients receiving colloid was found to be greater than that of crystalloid recipients by 4%, with a 95% CI of 0–8%. The corresponding relative risk of death was 1.19 (95% CI, 0.98–1.45). This difference was not significant since the 95% CI for relative risk included 1.

One of the major problems pervading this meta-analysis was that of heterogeneity among the included RCTs. Patients with any of various hypovolaemic insults received any of various colloids or crystalloids at differing concentrations. Yet the outcome of hypovolaemia is likely to be influenced by the cause of the hypovolaemia. There is, furthermore, little basis to postulate that different colloids, with disparate biochemical properties, will have similar effects on outcome. There is also little basis that different crystalloids can be considered similar in their potential effects on critically ill patients, or that varying colloid and crystalloid concentrations would have equivalent effects.

Excess mortality was reported in only five of the 19 RCTs included in the meta-analysis. Two of these, conducted by the same team of investigators, involved dextran in hypertonic saline compared with hypotonic saline in either the prehospital [26] or hospital setting [25]. These fluid regimens are certainly not representative of current practice. The report of the prehospital study also does not make it clear whether haemostasis was secured before plasma volume expansion. If it was not secured, then the volume expansion would have increased the risk of fatal haemorrhage.

The other three RCTs with excess mortality involved albumin. One death occurred among 14 albumin recipients in one RCT consisting of the pooled results from two series [11,17], whereas none of the six crystalloid patients died. It is difficult, with only a single albumin-associated death, to infer a meaningful mortality difference, especially since there were more than twice as many patients in the albumin group. Another of these RCTs [15] highlights an additional troublesome source of heterogeneity; namely,

between-group differences in severity of illness. Sepsis was present in 12/20 (60%) albumin patients compared with 12/26 (46%) crystalloid recipients in this study of patients with severe pulmonary insufficiency. The overall mortality rate for both groups combined was 21/24 (88%) in the presence of sepsis versus 3/22 (14%) in its absence. Consequently, the reported excess mortality in this study can probably be explained by the between-group disparity in frequency of sepsis rather than by the choice of resuscitation fluid. The final included RCT with reported excess mortality [12] compared 2.5% albumin with Ringer's lactate in burn patients. Hypo-oncotic 2.5% albumin is not a routinely used fluid in contemporary critical care, so again the relevance of this trial to current practice is uncertain.

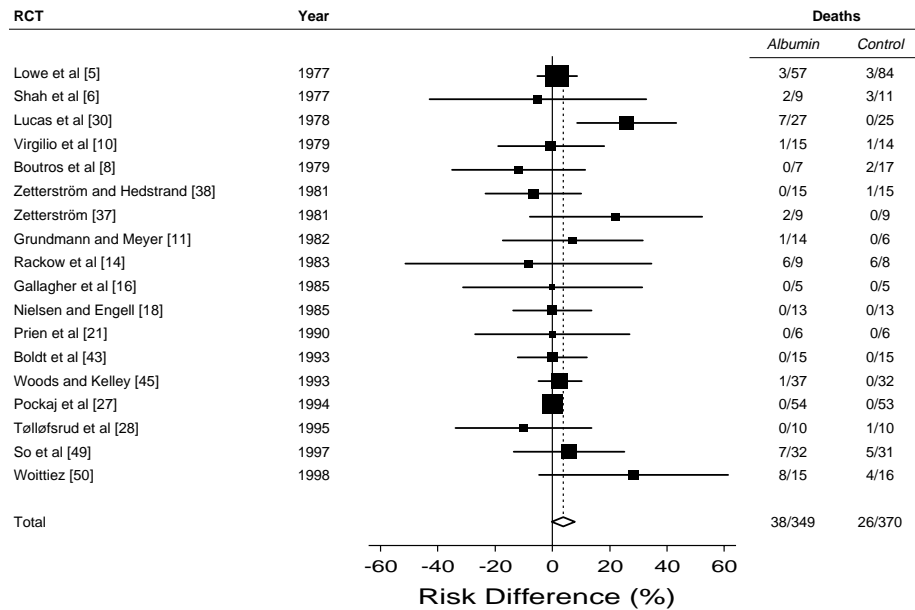
The colloid meta-analysis of Choi *et al* [3] involved 15 RCTs [5,8,10,12–15,20,22,27,30–34] with mortality data. Results derived from the use of various colloids and crystalloids in patients with varied hypovolaemic insults were also combined in this systematic review. The reported relative risk of death (1.16; 95% CI, 0.85–1.59) was similar to that found by Schierhout and Roberts [1]. Choi *et al* [3] were, however, more cautious in their interpretation of the meta-analytic results, concluding that there was no clear difference between colloids and crystalloids with respect to mortality.

Albumin meta-analysis

The Cochrane Injuries Group Albumin Reviewers (Cochrane Group) performed a meta-analysis of 30 RCTs [5,6,8–12,14,16,18,21,27,28,30,35–50] comparing administration of albumin with a regimen of crystalloid or no albumin in 1419 patients with varied characteristics, including neonates, and hypovolaemic insults [2]. The RCTs employed differing concentrations of albumin. Three categories of indications for albumin were distinguished: hypovolaemia, burns and hypoalbuminaemia. Overall excess mortality of 6% (95% CI, 3–9%) was documented in albumin recipients.

One noteworthy finding of the Cochrane Group meta-analysis was that, for RCTs of hypovolaemia (the category of most relevance for critical care physicians), the relative risk of death after albumin administration (1.46; 95% CI, 0.97–2.22) did not significantly exceed unity. The risk difference for these RCTs (4%; 95% CI, 0–8%) was also not statistically significant (Fig. 1). Relative risk was significantly above unity for the three included burns trials and the eight hypoalbuminaemia trials. However, the limited number of included burns RCTs makes firm conclusions regarding this indication difficult to reach. The hypoalbuminaemia trials are also problematic, since hypoalbuminaemia *per se* is less widely accepted currently as an indication for albumin administration than in past years. Furthermore, albumin was added to total parenteral

Figure 1



Mortality risk differences for hypovolaemia RCTs derived from the data of the Cochrane Group meta-analysis [2]. Negative risk difference values favour albumin, and positive values favour control. Error bars indicate 95% CI.

nutrition fluid in a number of these RCTs, and so there was potentially increased risk for fungal and bacterial contamination of the fluid and for particulate infusion with attendant embolic complications.

With respect to the 13 hypovolaemia RCTs considered by the Cochrane Group, a number of limitations similar to those of the colloid meta-analyses are apparent. The RCTs, as already indicated, were heterogeneous with respect to patient characteristics, hypovolaemic insult and treatment fluid composition. More than one-half of these RCTs reported only one or two total deaths [8,10,11,28,37,38,45]. Finally, the hypovolaemia RCT with by far the highest relative risk of death [30] entailed a fluid regimen that would clearly be judged excessive by current standards. Albumin group patients in this RCT received 12 l more fluid than their control group counterparts.

Shared limitations of the meta-analyses

The RCTs with mortality data included in all three recent meta-analyses are listed in Table 1. Two points evident from inspection of Table 1 are, first, that 26/47 RCTs (55%) were reported prior to 1990 and thus the meta-analyses relied heavily upon data unrepresentative of contemporary practice. The second point is that there were extensive differences in the sets of RCTs included in the three meta-analyses. The aims of the two colloid meta-analyses were similar; that is, to evaluate in a systematic fashion the outcomes of colloid administration in critically ill patients. It is reasonable to suppose that two systematic

reviews with similar aims would identify closely overlapping sets of RCTs. This was not, however, the case. Twenty of the 30 RCTs involving colloid administration (67%) were included in one colloid meta-analysis but not the other.

Furthermore, since albumin is a colloid, both colloid meta-analyses should arguably have included all the RCTs encompassed by the albumin meta-analysis. This was also not the case. Sixteen of the 30 RCTs in the albumin meta-analysis (53%) were absent from both colloid meta-analyses, and an additional eight (27%) were included in only one of the two colloid meta-analyses. Only 20% of these albumin trials were thus shared by all three meta-analyses. Three albumin RCTs [15,33,34] were also included by one or both colloid meta-analyses but not the albumin meta-analysis. These discrepancies in sets of included RCTs probably reflect, at least partly, differences in selection criteria adopted. It is nevertheless clear that none of the meta-analyses addressed the totality of relevant evidence.

All three meta-analyses included RCTs that were clearly heterogeneous from a clinical standpoint. Patients ranged from neonates to the elderly and differed substantially in the types of critical illness for which they required fluid administration. The included RCTs employed disparate fluids, in varying concentrations, to differing physiological endpoints. The meta-analyses failed to consider between-group differences in illness severity or the effects of concomitant therapies administered in the intensive care unit,

Table 1**RCTs with mortality data included in three recent meta-analyses**

RCT	Year	Meta-analysis		
		Schierhout and Roberts [1]	Choi <i>et al</i> [3]	Cochrane Group [2]
Bocanegra <i>et al</i> [4]	1966	•		
Bland <i>et al</i> [35]	1976			•
Lowe <i>et al</i> [5]	1977	•	•	•
Shah <i>et al</i> [6]	1977	•		•
Hall and Sorensen [7]	1978	•		
Lucas <i>et al</i> [30]	1978		•	•
Boutros <i>et al</i> [8]	1979	•	•	•
Jelenko <i>et al</i> [9]	1979	•		•
Virgilio <i>et al</i> [10]	1979	•	•	•
Nilsson <i>et al</i> [36]	1980			•
Moss <i>et al</i> [31]*	1981		•	
Zetterström [37]	1981			•
Zetterström and Hedstrand [38]	1981			•
Grundmann and Meyer [11]	1982	•		•
Goodwin <i>et al</i> [12]	1983	•	•	•
Modig [13]	1983	•	•	
Rackow <i>et al</i> [14]	1983	•	•	•
Shires <i>et al</i> [32]	1983		•	
Metildi <i>et al</i> [15]	1984	•	•	
Gallagher <i>et al</i> [16]	1985	•		•
Grundmann and Heistermann [17]	1985	•		
Nielsen and Engell [18]	1985	•		•
Sade <i>et al</i> [33]	1985		•	
Karanko [19]	1987	•		
Karanko <i>et al</i> [20]	1987	•	•	
Brown <i>et al</i> [39]	1988			•
Foley <i>et al</i> [40]	1990			•
Prien <i>et al</i> [21]	1990	•		•
Dawidson <i>et al</i> [22]	1991	•	•	
Kanarek <i>et al</i> [41]	1992			•
London <i>et al</i> [34]	1992		•	
Wojtysiak <i>et al</i> [42]	1992			•
Younes <i>et al</i> [23]	1992	•		
Boldt <i>et al</i> [43]	1993			•
Greenough <i>et al</i> [44]	1993			•
Nagy <i>et al</i> [24]	1993	•		
Vassar <i>et al</i> [25]	1993	•		
Vassar <i>et al</i> [26]	1993	•		
Woods and Kelley [45]	1993			•
Golub <i>et al</i> [46]	1994			•
Pockaj <i>et al</i> [27]	1994	•	•	•
Greenhalgh <i>et al</i> [47]	1995			•
Tølløfsrud <i>et al</i> [28]	1995	•		•
Wahba <i>et al</i> [29]	1996	•		
Rubin <i>et al</i> [48]	1997			•
So <i>et al</i> [49]	1997			•
Woittiez [50]	1998			•

*This RCT reported on a subset of patients included in Lowe *et al* [5]. Choi *et al* [3] elected to consider Moss *et al* [31] separately. Schierhout and Roberts [1] and the Cochrane Group [2] considered all the patients, including the subset reported by Moss *et al* [31], as part of the Lowe *et al* [5] RCT.

such as circulatory treatment with inotropes, vasopressors and vasodilators, as well as various protocols for respiratory management. The fluid management approach, importantly, was also not taken into account. Was a fluid challenge approach adopted? Were fluids administered in accordance with *a priori* formulae? Were the endpoints haemodynamic or biochemical? Did the fluid management strategy include attempts to minimize oedema? Such questions were left unaddressed by the meta-analyses.

Although all the included trials were randomized, very few adopted any form of blinding. The possibility of biased results therefore cannot be dismissed.

Finally, the between-group differences in mortality reported by all three meta-analyses were minor. In the absence of clear-cut fluid-associated differences and in view of their numerous shared limitations, the meta-analyses do not provide a compelling basis for critical care physicians to embrace particular fluid management approaches.

Discussion

The recent meta-analyses have served to reignite the perennial debate as to the comparative merits of colloids and crystalloids. Framing the debate in these terms, however, places the focus on *what* fluid is used rather than on *how* it is used. It is very clear that either crystalloid or colloid can be harmful if administered in insufficient or excessive amounts. The key issue is to use fluids skillfully, taking into account their specific properties and administering them in appropriate quantities to haemodynamic endpoints. Favourable results can be obtained, for example, by a fluid challenge approach designed to maintain the plasma volume at a level that optimizes stroke output of the heart.

It should also be borne in mind that use of colloids and crystalloids is by no means mutually exclusive. Indeed, most patients requiring fluids will probably receive crystalloid. The question then becomes whether colloid should be added to the fluid regimen. The volume administered will need to be at least three-fold greater than that of colloid to achieve comparable expansion of the intravascular compartment if crystalloids are to be relied upon exclusively. Colloids can be administered in smaller volumes and also serve to increase colloid osmotic pressure. Colloids are also retained in the circulation at least for the 5–10-min period needed to perform the measurements of haemodynamic variables that are essential for implementing a fluid challenge approach. Retention of crystalloid in the circulation for this minimum period is by no means assured in patients with extensive vascular leakage.

The supposition that choice of resuscitation fluid might exert a substantial impact on patient mortality is implicit in the design of the recent meta-analyses. The fluid-related

differences in mortality documented by the meta-analyses were relatively small. These findings are unsurprising, since mortality is most probably affected far more powerfully by the pathophysiology and severity of the patient's illness, the array of other treatments rendered and the fluid management approach adopted than by the selection of fluid *per se*.

The authors of two of the meta-analyses called for RCTs to be conducted that might resolve the question whether fluid choice significantly affects mortality [1,2]. The requirements for a RCT addressing this issue would, however, be sobering. If a control group mortality of 20% is assumed and 97.5% power were desired to detect excess colloid-associated mortality of at least 4% at the 0.05 α level, then 6584 patients would need to be recruited, or 4611 patients to establish equivalence. The number of patients would be even higher if lower control group mortality were assumed. Furthermore, the patients would need to be similar in type and severity of illness. It would be important to compare a single colloid with a single crystalloid administered at the same respective concentrations to the same endpoints by the same fluid management protocols. Circulatory and respiratory management protocols would need to be comparable. Such a RCT would obviously require the commitment of daunting healthcare resources. Given the expectation that choice of fluid may have little or no effect on mortality, it is highly questionable whether such a RCT would be a wise investment.

Could the possibility of poorer outcomes with colloids, as raised by two of the meta-analyses, simply be circumvented by switching to crystalloids? Such a change in fluid management practice would not be trivial. The goals and methods of fluid therapy would need to be completely reassessed. The need to tolerate crystalloid-induced oedema and its corresponding problems would need to be accepted. Circulatory and respiratory support might need to be altered. Exclusive reliance on crystalloid might, for instance, prompt increased use of inotropes and pressors or adjustment of respirator settings to provide a higher level of positive end-expiratory pressure. Implementing such changes would also require a thorough re-education process for the entire intensive care unit team, a process itself not free of risk. Since the available evidence of colloid-associated excess mortality is far from unequivocal, there is little justification for major changes in fluid management practice based simply upon the recent meta-analyses. An issue of greater importance than small or even non-existent mortality risk differences is, arguably, whether a particular fluid allows the intensive care unit to provide better patient care.

Conclusion

The results of recent meta-analyses suggest that the effect of resuscitation fluid choice on mortality, if any, is

minor. Furthermore, the meta-analyses need to be interpreted with caution due to methodological limitations. The meta-analyses do not provide a sound rationale for altering current fluid management practice.

Commentary

Jean-Louis Vincent, MD, PhD: The primary advantages of colloids are, first, that only a third or less the volume needs to be administered to achieve the same resuscitation endpoints compared with crystalloids and, second, that there is less oedema. However, the need to administer a larger volume is not necessarily a serious limitation, and oedema might not be harmful at least in the near term. Is the presence of interstitial oedema potentially harmful in terms of oxygen availability to the cells, wound healing or decubitus ulcers?

Andrew R Webb, MD: It depends on degree. The presence of some interstitial oedema may not create any serious problems. It also depends on the type of patient. Young trauma patients with gunshot wounds may tolerate massive oedema without adverse sequelae. But in the elderly patient who may be susceptible to decubitus ulcer formation or prone to heart failure, oedema should probably be avoided. The oedema may, for instance, compromise myocardial function in such patients. Lastly, for sepsis patients with capillary leakage and massive oedema, it is probably of great importance that the fluid management approach be geared toward minimizing oedema.

Uwe Kreimeier, MD: In a recently reported RCT of sepsis patients receiving normal saline or 5% albumin, the expansion of the extracellular compartment in the albumin group equalled twice the infused volume [51]. So there appears to be a fluid volume effect on the interstitium when albumin is infused in these patients.

Andrew R Webb, MD: That observation has been extensively discussed. There is no doubt that infusing excessive amounts of colloid can cause interstitial fluid overload. Moreover, all the colloids are subject to extravasation in states of capillary leakage such as sepsis. The objective is to infuse the correct volume of colloid, thereby avoiding oedema formation, and it is clearly possible to achieve this objective in many patients. If oedema is kept to a minimum, it is unlikely that substantial volumes of colloid will occupy the interstitial space and contribute to fluid efflux from the plasma space.

William J Sibbald, MD: It is generally possible to achieve physiologic endpoints more rapidly with colloid than crystalloid. This rapidity may, for example, be advantageous in elderly patients.

The heterogeneity of the RCTs in the meta-analyses really should be emphasized. A septic patient is clearly unlike an

ischaemia-reperfusion trauma patient. For instance, lymphatic flow is much different in a trauma than a sepsis patient. In sepsis, lymphatic propulsive activity is depressed, and therefore interstitial fluid is cleared with greater difficulty. In the trauma patient, this activity is enhanced. Combining these very different types of patients in the same meta-analysis is a questionable approach.

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