FLUID RESUSCITATION

SUMMARY

The decision as to whether to use crystalloid versus colloid as the primary resuscitation fluid in the critically ill has long been a subject of debate. Two previous meta-analyses of the numerous prospective, clinical trials in this area suggested that colloid resuscitation may be associated with increased patient mortality. A large multicenter, randomized, double-blind trial, however, documented the safety of colloid-based resuscitation using albumin, but failed to demonstrate either an economic or survival benefit to such therapy.

RECOMMENDATIONS

- **Level 1**
  - **Despite equivalent efficacy, crystalloids are the resuscitation fluid of choice given the lack of survival benefit and increased cost associated with albumin.**
  - **Albumin is contraindicated in the initial resuscitation of the traumatically injured.**
  - **Albumin should be avoided in patients with severe traumatic brain injury (Glasgow Coma Score (GCS) ≤ 8).**
- **Level 2**
  - **Non-protein colloids, specifically hydroxyethyl starch (HES), has been associated with increased rate of renal injury, including renal insufficiency and renal failure requiring renal replacement therapy.**
- **Level 3**
  - **Colloids may have a secondary role in patients unresponsive to crystalloids or those who cannot tolerate large-volume crystalloid resuscitation.**

INTRODUCTION

Critically ill patients frequently demonstrate evidence of inadequate tissue perfusion manifested by anaerobic metabolism and lactic acidosis. The primary resuscitation goal in such patients is to restore tissue perfusion / cellular oxygenation and maintain end-organ function through volume resuscitation. The optimal resuscitation fluid, however, remains a subject of debate.

Crystalloids

Crystalloids may be classified as hypotonic, isotonic, or hypertonic. For purposes of resuscitation, only the isotonic and hypertonic fluids are of use as hypotonic fluids (such as 5% dextrose in water and ½ normal saline) do not remain intravascular. Isotonic fluids (such as lactated Ringer's and normal saline) form the backbone of crystalloid resuscitation. Hypertonic fluids (such as 3%, 6%, or 7.5% normal saline) may have a role in specific patient populations such those with traumatic brain injury. Crystalloids have the advantage of being inexpensive and readily available. They resuscitate both the intravascular and

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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interstitial space, and promote urinary output. Disadvantages include edema formation in patients with capillary permeability and the need for increased volumes to achieve equivalent resuscitation to colloids.

Colloids

Colloids may be divided into protein and non-protein colloids. The protein colloids include human serum albumin (5% and 25%) and gelatin solutions (Plasmagel, Haemacell, Gellifundol). The latter are not currently available in the US and will therefore not be addressed further. Albumin has the advantage of remaining intravascular longer than the crystalloids; less volume is therefore required. Albumin is expensive (65 times that of an equivalent volume of crystalloid) and does not restore the interstitial space. It can cause anaphylaxis in rare circumstances.

The non-protein colloids include the starches (6% hetastarch, 10% pentastarch) and the dextrans (dextran-40 in normal saline, dextran-70 in 5% dextrose in water). Previously, they have been found to be equivalent to albumin as a resuscitation fluid, and their use was discouraged due primarily to their increased expense (13 times that of crystalloid), a dose-related coagulopathy (greatest with hetastarch), and occasional anaphylaxis (greatest with the dextrans). However, studies have demonstrated a significant increase in renal injury resulting in renal insufficiency and, in some patients, renal failure requiring renal replacement therapy for patients receiving hydroxyethyl starch (HES) compared to saline alone. Moreover, non-protein colloids can also interfere with antigen detection during cross matching of blood products. As such, the use of these products, most specifically HES, has been discouraged in the resuscitation of hypovolemic patients.

There is no debate that 1) colloids remain intravascular longer than crystalloids, 2) colloids expand plasma volume to a greater extent, and 3) crystalloids are more likely to cause edema formation. The real question is whether colloids improve patient morbidity and mortality and whether their use is worth the added expense.

LITERATURE REVIEW

Several meta-analyses of prospective, randomized clinical trials evaluating the use of crystalloids vs. colloids in critical care resuscitation were performed in the 1990's (1-4). Each demonstrated a survival advantage to patients resuscitated with crystalloids, especially in the traumatically injured. These studies (including two performed by the Cochrane Group) consistently concluded that there is no advantage to colloid resuscitation and that crystalloids are the resuscitation fluid of choice, especially in patients following trauma, sepsis, acute respiratory distress syndrome (ARDS), or increased capillary permeability. The potential for increased mortality (4-6%) in these studies among patients resuscitated with albumin led several authors to call for a review of its use by the FDA. Interestingly following the meta-analyses published by Schierhout and Roberts in the *British Medical Journal* in 1998, use of albumin solutions in the United Kingdom reportedly decreased by at least 40%.

The vigorous outcry that followed the Cochrane meta-analyses prompted several additional studies. In 2001, Wilkes and Navickis performed a comprehensive meta-analysis concerning the use of albumin versus crystalloid in critically ill patients (5). They evaluated 55 studies including 3504 randomized patients (27 studies with 1504 surgical/trauma patients). The pooled relative risk of death for all patients was 1.11 (95% CI, 0.95-1.28) and for surgery and trauma patients was 1.12 (95% CI, 0.85-1.46). Although no statistically significant increase in mortality was seen, the point estimate indicates an increase in relative risk of death of more than 10% for surgical and trauma patients.

In 2003, Rizoli et al. published an excellent review of some of the larger meta-analyses and of the methodology used in these studies themselves (6). They concluded that "even when all limitations and nuances of interpretation are considered, one piece of evidence that comes out is that trauma patients should probably continue to be resuscitated with crystalloids." They stressed that the results of these meta-analyses should, in the very least, be "hypothesis generating" and should fuel further, larger, randomized controlled trials. Another such critical appraisal can be found in an editorial by Cook and Guyatt (7). Many other reviews have recently been published on this subject as well (8,9).

In 2004, the SAFE Study Investigators published a very large (~7000 patient) multicenter, randomized, double-blind trial comparing 4% albumin (n=3497) to normal saline (n=3500) for intravascular-fluid resuscitation (10). This study found no difference in mortality, ICU or hospital days, days of mechanical ventilation, or days of renal-replacement therapy. It was noted that patients who were resuscitated with albumin received less overall fluid. Additionally, the study also found that the ratio of crystalloid to colloid administration to achieve the same resuscitation end points was much less than previously thought, with a ratio of albumin to saline administration of 1:1.4, as compared to the previously adopted ratio of 1:3. Subgroup analysis noted that the relative risk of death among trauma patients in the albumin group was 1.36 compared to the saline group. Among traumatically injured patients without head injury there was no difference in mortality. The group concluded that albumin and saline should be considered clinically equivalent treatments for intravascular volume resuscitation in a heterogeneous population of patients in the ICU. Performed in the setting of a national health service (Australia and New Zealand), no economic analysis was completed. While the SAFE Study authors purport that this study demonstrates that albumin should be utilized as a resuscitation fluid, the lack of a survival benefit of albumin and the significant economic burden associated with its use outside of a nationalized health service suggests that albumin should be reserved for specific, limited indications.

The SAFE Study authors subsequently performed a *post hoc* analysis of their data to confirm the suggestion that albumin is associated with a higher mortality rate in patients with traumatic brain injury (TBI) (11). At 24 months post-study, 33.2% of albumin patients had died vs. 20.4% of crystalloid patients (relative risk 1.63; 95% confidence interval 1.17 to 2.26; p=0.003). The relative risk was 1.88 for patients with a Glasgow Coma Score (GCS) of 3-8 (95% confidence interval 1.31 to 2.70; p<0.001) and 0.74 for patients with a GCS of 9-12 (95% confidence interval 0.31 to 1.79; p=0.50). The authors concluded that resuscitation with albumin is associated with a higher mortality rate among patients with severe TBI.

In 2013, the CRISTAL study evaluated the effects of colloid resuscitation versus crystalloid resuscitation in patients with hypovolemic shock in a randomized controlled prospective study (12). The two groups were stratified and outcomes were analyzed, including mechanical ventilation days, need for vasopressor therapy, ICU and hospital stay, and organ failure. The two groups were similar in injury severity score and ICU admission type. Neither 28 day mortality nor length of ICU stay were statistically different between each group. There was a reduction in the 90 day mortality was slightly lower in patients stratified to the colloid resuscitation group (RR 0.92, 95% CI 0.86 to 0.99, p = 0.03); however, the authors stated that these findings should be considered exploratory and required further evaluation. The study did find that patients who received crystalloid resuscitation were placed on mechanical ventilation earlier compared to patients receiving colloids only (mean 2.1 vs 1.8 days respectively, mean difference 0.30 [95% CI 0.09 to 0.48] days; p = 0.01). However, there was no statistical difference in need for renal replacement therapy, development of organ failure, or hospital length of stay between the two groups.

Non-protein colloids, including Hydroxyethyl starch (HES), had previously been found to be equivalent to albumin as a resuscitation fluid. However, according to the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), published in 2013, the use of HES was associated with a statistically increased rate of adverse events (5.3% vs 2.8%, p<0.001) (13). The researchers looked at the use of saline only resuscitation versus HES/saline solutions (Voluven). Patients were randomized to each group, and outcome data, including 90 day mortality and all adverse events, were analyzed. Each group had similar characteristics and injury severity score. The 90 day mortality between each group was not statistically significant; however, the development of renal insufficiency and injury was statistically greater in the HES group (RR 0.91, p=0.007). Additionally, the need for renal-replacement therapy was statistically greater for patients receiving HES (RR 1.21, p=0.04). As the use of HES was not found to have any survival benefit when compared to saline only, and was actually associated with increased renal failure in these patients, its use has significantly decreased and been discouraged in favor of saline or other colloid solutions, including albumin.

The most recent Cochrane Database Review (78 randomized controlled trials, including the SAFE study and CHEST study) published in 2013 reached a similar conclusion to previous database reviews, stating that “as colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.” (14).

Additionally, they concluded that the use of HES was actually associated with worse outcomes, including increased mortality. Twenty four trials compared albumin to crystalloid with a pooled RR of 1.01 (95% CI 0.93 to 1.10). Twenty five studies compared HES with crystalloids (RR 1.1, 95% CI 1.02 to 1.19), 11 trials compared modified gelatin (RR 0.91, 95% CI 0.49 to 1.72), and 9 trials compared dextran (RR 1.24, 95% CI 0.94 to 1.65).

Several excellent review articles and consensus statements on this issue have previously been published (15-16). From these documents, and the above cited trials, the following general statements can be made:

- Crystalloids
  - Are as effective as albumin in post-operative patients
  - Are the initial resuscitation fluid of choice for:
    - Hemorrhagic shock / traumatic injury
    - Septic shock
    - Hepatic resection
    - Thermal injury
    - Cardiac surgery
    - Dialysis induced hypotension

- Non-protein colloids
  - Should be avoided due to increased risk of renal injury leading to need for renal replacement therapy.

- Albumin
  - Should be considered a second-line agent
  - Does not provide benefits over crystalloid alone when used for intravascular expansion
  - Titrated to maintain pre-determined levels is not supported by the literature
  - Is contraindicated in the first 24 hours post-burn, but may have a role in severe burns (>50%TBSA) after the first 24 hours
  - Administered in combination with parenteral nutrition does not provide benefit
  - May be useful in:
    - Elderly patients who cannot tolerate large volume resuscitation
    - Following paracentesis of greater than 4 L
    - Severe diarrhea and albumin <2 g/dl
    - Nephrotic syndrome
    - Liver transplant patients with albumin < 2.5 g/dl
    - Following plasmapheresis

REFERENCES

1. Velanovich V. Crystalloid versus colloid fluid resuscitation: A meta-analysis of mortality. *Surgery* 1989;105:65-71.
2. Schierhout G, Roberts L. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998; 316:961-964.
3. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ*. 1998; 317:235-240.
4. Choi PTL, Yip G, Quinonez LG, et al. Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med* 1999; 27:200-210.
5. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2001; 135: 149-164.
6. Rizoli SB. Crystalloids and Colloids in Trauma Resuscitation: A Brief Overview of the Current Debate. *J Trauma* 2003; 54: S82-S88.
7. Cook D, Guyatt G. Colloid use for fluid resuscitation: evidence and spin. *Ann Intern Med*. 2001; 135: 205-208.
8. Boldt J. New Light on Intravascular Volume Replacement Regimens: What Did We Learn from the Past Three Years? *Anesth Analg* 2003; 97: 1595-604)
9. Boldt J. Fluid choice for resuscitation of the trauma patient: a review of the physiological, pharmacological, and clinical evidence. *Can J Anesth* 2004; 51: 500-513.

10. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350: 2247-56.
11. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *NEJM* 2007; 357:874-884.
12. Annane, D, 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(17): 1809-1817.
13. Myburgh, JA, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *NEJM* 2012; 367:1901-1911.
14. Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013;

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