Disclosures

Compensated contractual services to the biotherapeutics industry, including the manufacturers of products described in this lecture
Physiologic Functions of Albumin

- Accounts for 50-60% of plasma proteins
- Creates 75% of colloid osmotic pressure
  - Colloid osmotic pressure (COP) ≈ 20 mm Hg for 4-5% albumin
    (5x = 100 mm Hg for 25% albumin)
- 60% of total albumin mass is extravascular
- Reversibly binds cations and anions
- Transport and inactivation of drugs, metals, dyes, fatty acids, hormones, enzymes, bilirubin
- Albumin is the principal extracellular antioxidant found in plasma

ALBUMIN vs OTHER COLLOIDS
POST-PARACENTESIS CIRCULATORY DYSFUNCTION

INDICATES THAT ALBUMIN’S BENEFIT IS NOT JUST THROUGH VOLUME EXPANSION

Sort et al NEJM 1999
Key questions

- Which conditions should I treat with albumin?
  - (For what is it approved by authorities?)

- What alternatives are available?

- How is it going to affect medical costs?
“New clinical efficacy data are not ordinarily required for the approval of new therapeutic albumin (natural source) products for existing indications ……[albumin] has a well-established safety and efficacy profile because of our extensive clinical experience with the product. Approvals of albumin products have been based primarily on conformance to the product and manufacturing standards described in the regulations and performance of the products in small safety trials “

Recently approved albumin products – FDA – Kedrion 2011

- Hypovolemia: Restoration and maintenance of circulating blood volume where volume deficiency is demonstrated and colloid use is appropriate.
- Hypoalbuminemia: When the albumin deficit is the result of excessive protein loss, the effect of albumin administration will be temporary.
- Prevention of central volume depletion after paracentesis due to cirrhotic ascites.
- Ovarian hyperstimulation syndrome (OHSS).
- Adult Respiratory Distress Syndrome (ARDS).
- Burns
- Hemodialysis: For patients undergoing long term dialysis or are fluid-overloaded.
- Cardiopulmonary Bypass Procedures: As part of the priming fluid.

The CMC assessments have been the basis for approval of Albumin (Human) products without requiring new preclinical or clinical studies.
Indications - Summary of Basis of Approval

- Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.
- The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient.

Indications - Package Insert

- INDICATIONS AND USAGE
  - 1.1 Hypovolemia
  - 1.2 Hypoalbuminemia
  - 1.3 Prevention of Central Volume Depletion after Paracentesis due to Cirrhotic Ascites (Treatment Adjunct)

- FDA requested a clinical trial under an IND to show non-inferiority relative to human albumin brand (25%) licensed in the US in preventing central volume depletion after paracentesis due to cirrhotic ascites.
- Due to the SAFE Study and the extensive post-marketing safety experience with Octapharma's albumin preparations, the study was terminated prematurely in agreement with the FDA.
30 RCTs in systematic review

1419 critically ill patients

All indications included

All doses and concentrations

Any control group (nothing, saline, Ringers, dextrose/Ringers)

No protocols of care

Limited assessment of quality

### The Cochrane Review

<table>
<thead>
<tr>
<th>Type of injury</th>
<th>No of deaths</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowe et al</td>
<td>3/57</td>
<td>1.47 (0.31 to 7.05)</td>
<td>4.0</td>
<td>1.47 (0.31 to 7.05)</td>
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<tr>
<td>Shah et al</td>
<td>2/9</td>
<td>0.81 (0.17 to 3.87)</td>
<td>4.5</td>
<td>0.81 (0.17 to 3.87)</td>
</tr>
<tr>
<td>Lucas et al</td>
<td>7/27</td>
<td>13.93 (0.84 to 231.94)</td>
<td>0.9</td>
<td>13.93 (0.84 to 231.94)</td>
</tr>
<tr>
<td>Virgilio et al</td>
<td>1/15</td>
<td>0.93 (0.06 to 13.54)</td>
<td>1.7</td>
<td>0.93 (0.06 to 13.54)</td>
</tr>
<tr>
<td>Boutros et al</td>
<td>0/7</td>
<td>0.45 (0.02 to 8.34)</td>
<td>2.5</td>
<td>0.45 (0.02 to 8.34)</td>
</tr>
<tr>
<td>Zetterstrom et al</td>
<td>0/15</td>
<td>0.33 (0.01 to 7.58)</td>
<td>2.5</td>
<td>0.33 (0.01 to 7.58)</td>
</tr>
<tr>
<td>Zetterstrom et al</td>
<td>2/9</td>
<td>5.00 (0.27 to 91.52)</td>
<td>0.8</td>
<td>5.00 (0.27 to 91.52)</td>
</tr>
<tr>
<td>Grundmann et al</td>
<td>1/14</td>
<td>1.40 (0.06 to 30.23)</td>
<td>1.1</td>
<td>1.40 (0.06 to 30.23)</td>
</tr>
<tr>
<td>Rackow et al</td>
<td>6/9</td>
<td>0.89 (0.48 to 1.64)</td>
<td>10.5</td>
<td>0.89 (0.48 to 1.64)</td>
</tr>
<tr>
<td>Woods et al</td>
<td>1/37</td>
<td>2.61 (0.11 to 61.81)</td>
<td>0.9</td>
<td>2.61 (0.11 to 61.81)</td>
</tr>
<tr>
<td>Tollefsrud et al</td>
<td>0/10</td>
<td>0.33 (0.02 to 7.32)</td>
<td>2.5</td>
<td>0.33 (0.02 to 7.32)</td>
</tr>
<tr>
<td>So et al</td>
<td>7/32</td>
<td>1.36 (0.48 to 3.82)</td>
<td>8.4</td>
<td>1.36 (0.48 to 3.82)</td>
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<tr>
<td>Woltering et al</td>
<td>8/15</td>
<td>2.13 (0.81 to 5.64)</td>
<td>6.4</td>
<td>2.13 (0.81 to 5.64)</td>
</tr>
</tbody>
</table>

Subtotal: 38/256: 26/278

\[ \chi^2 = 9.45 \text{ (df=12)} \]

Totally discredited through other MA’s and trials

FDA – Trigger happy

- Cochrane meta-analysis published in **July 25, 1998** issue of the BMJ
- FDA Letter to Healthcare Providers on **August 19, 1998**
  - Serious concern over the safety of albumin administration
  - Treating physicians to exercise discretion in its use.
- Flaws in Cochrane MA - Ignored
- Other MA’s contradicting Cochrane - Ignored
- Trials showing different findings - Ignored
- SAFE study – Led to FDA retracting its Letter – 6 years after it was issued
Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate. The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.

To (Proposed revision)

Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.
Proposed trial 2010 – Effect of albumin infusion in liver disease with infection – Spontaneous Bacterial Peritonitis (SPG) UCL (Jalan et al)

Presentation with evidence of infection

- Proposed as a Phase 2B trial to MHRA
- Agency response
  - Considers indication an extension of the approved indication (volume expansion)
  - Therefore accepts trial as a Phase 4 – Post-market - study

- Primary outcome: Organ failure during the 12 weeks period post randomization
- Secondary outcomes: death within 3 months post randomization, length of stay, changes in albumin biology during the course of the illness

SMT = Standard Medical Treatment
Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis

Nicolai Haase, physician, Arcadia Pomer professor, Louis Inojer Hennings physician, Martin Siegmund professor, Bo Lauridsen physician, Mik Wetterslev medical student, Jerri Wetterslev chief physician

Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy

Amit Patil
Umerjaved Waleed
Stephen J. Brett

Randomised trials of 6% tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis

Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation: A Systematic Review and Meta-analysis

Syan Zarcohnski, MD, MSc
Ahmed M. Abou-Setta, MD, PhD
Aless P. Tourke, MD, MSc
Brett L. Houston, RSc
Lauralyn McIntyre, MD, MSc
John C. Marshall, MD
Dean A. Ferguson, PhD, MHA

The University of Western Australia
“Based on available evidence there is no clear benefit of HES over other available IV resuscitation solutions with potential risks for increased bleeding and renal toxicity; HES behaved as a class in terms of their toxic effects on bleeding and renal failure.”
Review of HES by the EMA

Timetable for the procedure

Referral under article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Hydroxyethyl starch containing medicinal products, solution for infusion

Procedure no: EMEA/H/A-3/1248

<table>
<thead>
<tr>
<th>Procedural step</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification</td>
<td>20 November 2012</td>
</tr>
<tr>
<td>Start of the procedure (PRAC):</td>
<td>December 2012 PRAC (26-29 November 2012)</td>
</tr>
<tr>
<td>List of Questions (LoQ):</td>
<td>29 November 2012</td>
</tr>
<tr>
<td>Submission of responses:</td>
<td>04 February 2013</td>
</tr>
<tr>
<td>Re-start of the procedure:</td>
<td>11 February 2013</td>
</tr>
<tr>
<td>Rapporteur and Co-rapporteur assessment report(s) circulated to PRAC and to CMDh:</td>
<td>08 April 2013</td>
</tr>
<tr>
<td>Comments:</td>
<td>22 April 2013</td>
</tr>
<tr>
<td>Updated Rapporteur and Co-rapporteur assessment report(s) circulated to PRAC and to CMDh:</td>
<td>02 May 2013</td>
</tr>
<tr>
<td>PRAC List of Outstanding Issues (LoOI)/PRAC Recommendation:</td>
<td>May 2013 PRAC</td>
</tr>
</tbody>
</table>
Albumin can ameliorate the disturbed microcirculatory effects of sepsis


INTRODUCTION

Sepsis is a systemic, deleterious host response to infection leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) and septic shock (severe sepsis plus hypotension not responsive to fluid resuscitation) [1]. Mortality is about 33.3% in the patients with severe sepsis who are hospitalized [2] treated with the current standard of care in the US. Hypoalbuminemia is a feature of sepsis which is treated with fluids. Among several fluid treatments available for treating sepsis, the first line of treatment is generally crystalloids in a range of volumes. Colloids, including albumin and hydroxyethyl starch are also widely used. Recent large randomized clinical trials (RCTs) provide insight in determining the efficacy of the fluids used in treatment of sepsis. A number of adverse events have been associated with HES including hemodilutional, hemodynamic and renal dysfunction.

In this study, we have conducted a network meta-analysis [3] and have combined the mortality outcomes from selected randomized clinical trials. A Bayesian analysis ranked the treatments and provided probability of being the most effective treatment for septic shock.

METHOD

A literature search of human clinical trials was conducted in PubMed, ClinicalTrials.gov and within the bibliographies of other relevant systematic reviews. In addition, data for mortality for treatment and interventions for the few trials for albumin in septic shock were extracted from the results presented in conferences, peer reviewed articles and abstracts.

The search terms used were sepsis, septicemia, systemic inflammatory response syndrome, septic shock, fluid therapy, resuscitation, plasma substitute, albumin, serum albumin, starch, hydroxyethyl starch, hetastarch, pentastarch, tetraastarch and mortality. The studies were first abstracts done by a reviewer (MB). In the second screening, two reviewers (AF, MB) were involved. In this screening, full texts were reviewed and articles were included if the baseline characteristics and outcomes were described in all patients or no mortality results (Figure 1). The chosen studies were validated. The trials were all double-blinded, Ringer’s lactate was included in which mentioned crystalloids were included to represent crystalloids in the analysis.

In the base case, all formulations of crystalloids, HES and albumin were assumed to be the pharmacologically equivalent. The effective sample size used was assumed to be the same across different age groups. The mortality data for the longest follow-up in a trial were included in the analysis. The trials which had data for patients with severe sepsis, septic shock and sepsis as a sub-group were included.

The indirect comparison between crystalloid, albumin and HES trials was conducted using the Bayesian method for binomial likelihood. A fixed effects network meta-analysis was conducted for the mortality as well as a reference treatment compared to any composition of colloid fluid. Stelman, et al. 2011 [3] used the same method for the analysis. A random effects model was also used for the analysis. The choice for fixed or random effect model was made by assessing model deviance information criteria (DIC) and standard deviation between the trials for the consistency models. The consistency model compared the three trials included, whereas the random effects model compared the three closely measured trials. The odds ratio and corresponding 95% credible intervals were obtained with 50,000 iterations and convergence was seen around 15,000.

RESULTS

In the literature search, 391 studies were identified. 336 of these were excluded in the first screening. 13 studies were finally included in the analysis. DIC was 182.5 for random effects model and 160.7 for fixed effects model. The standard deviation of random effects model was more than fixed effect model at 17.2 vs. 15.1. The standard deviation with random effect was also used as a measure of the goodness of fit for the model. DIC was used to fit the data better. The assessment showed similar effect sizes and DICs for the three models and consistency models in case of the fixed suggested systematic consistency.

CONCLUSION

This is the first network meta-analysis on risk of mortality in fluid resuscitation among the most common severe sepsis comparing the three closely measured trials. Albumin as a fluid therapy in sepsis is associated with the lowest mortality of the three modalities studied. These results are relevant to strategies for fluid treatment in intensive care.

BIBLIOGRAPHY

(Insert References Here)

Figure 1: Study Flow Diagram

Figure 2: Forest plot of results of Bayesian fixed effect network meta-analysis

Figure 3: Bar plots for the ranking probabilities of competing fluid treatments. The horizontal axis is the possible rank of each treatment (from best to worse). The size of each bar corresponds to the probability of each bar to be at specific rank.

TABLE 1: Basic characteristics of the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBIOS 2012</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>Hospital discharge</td>
</tr>
<tr>
<td>Nyhus et al. CHEST study 2013</td>
<td>Severe sepsis</td>
<td>Crystalloid, HES</td>
<td>90 day</td>
</tr>
<tr>
<td>Brunkhorst (VIBP)</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>90 day</td>
</tr>
<tr>
<td>Capart et al. (PATS2) Intensive Care Med 2011</td>
<td>Severe sepsis</td>
<td>Albumin</td>
<td>90 day</td>
</tr>
<tr>
<td>Stelman et al. Hepatogastroenterology 2011</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>90 day</td>
</tr>
<tr>
<td>Gudet et al. (CRYSTMAD) Critical Care 2012</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>90 day</td>
</tr>
<tr>
<td>Metalland et al. British Journal of Anaesthesia 2012</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>90 day</td>
</tr>
<tr>
<td>Brunkhorst et al. (SAFE study) BMJ 2004</td>
<td>Severe sepsis</td>
<td>Crystalloid</td>
<td>90 day</td>
</tr>
<tr>
<td>Mironov et al. (PINNEX) Can J Anaesth 2004</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>90 day</td>
</tr>
<tr>
<td>Perrier et al. N Engl J Med 2012</td>
<td>Severe sepsis</td>
<td>Crystalloid</td>
<td>90 day</td>
</tr>
<tr>
<td>Van Heusen &amp; Bhan 2012</td>
<td>Severe sepsis</td>
<td>Crystalloid, Albumin</td>
<td>90 day</td>
</tr>
</tbody>
</table>
Network MA for studies in sepsis
Ranking probabilities of competing fluid treatments

<table>
<thead>
<tr>
<th></th>
<th>Rank 1</th>
<th>Rank 2</th>
<th>Rank 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>96.38%</td>
<td>3.60%</td>
<td>0.00%</td>
</tr>
<tr>
<td>Crystalloid</td>
<td>3.61%</td>
<td>96.27%</td>
<td>0.00%</td>
</tr>
<tr>
<td>HES</td>
<td>0.01%</td>
<td>0.00%</td>
<td>99.87%</td>
</tr>
</tbody>
</table>

Bansal et al 2013
Decision tree to assess cost-effectiveness

Fluids in sepsis

ICU Fluid therapy in sepsis

LEgenpop = 18.6
  c.Alb = 270
c.HES = 269
c.Renal = 142404
c.SepsisGen = 18199
  p.Bleed = 0.063
  p.BleedHES = 0.095
  p.DeadAlb = 0.309
  p.DeadHES = 0.385
  p.DeadSep = 0.333
  p.Renal = 0.16
  p.RenalHES = 0.225

Crystallloid
  Survival
  #
  Death
    p.DeadSep

Albumin
  Survival and discharge
  #
  Death
    p.DeadAlb

HES
  Survival
  #
  No Renal
  #
  No Bleeding

Renal
  p.RenalHES
  No Bleeding
  #
  Bleeding
    p.BleedHES
  No Bleeding
    #
## Results of cost-effectiveness analysis

<table>
<thead>
<tr>
<th></th>
<th>Total Medical Cost</th>
<th>Effectiveness *</th>
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</thead>
<tbody>
<tr>
<td>Crystalloid</td>
<td>$18,199</td>
<td>Reference</td>
</tr>
<tr>
<td>Albumin</td>
<td>$18,469</td>
<td>0.118</td>
</tr>
<tr>
<td>HES</td>
<td>$38,274</td>
<td>-0.188</td>
</tr>
</tbody>
</table>

* Years saved/lost compared to crystalloid.
Summary and Conclusions

- Albumin’s oversight by regulators has focused on safety
- Approved indications are limited to hypovolemic disease states
- Many proposed indications for albumin may be interpreted through the currently approved conditions
- Regulators have lacked any urgency in assessing the issues around HES
- Albumin, in certain circumstances, is a cost-effective therapy.
- Clinical access to albumin should not be impeded by regulation or cost