Critical Review Form
Therapy

Phase II trial on the use of Dextran 70 or starch for supportive therapy in Kenyan children with severe malaria, *Crit Care Med* 2010; 38: 1630-1636

Objectives: **"To establish whether hypovolemic shock manifesting as acidosis in severe malaria can be safely corrected by volume replacement with Dextran (6% Dextran 70) or HES (6% hydroxyl ethyl starch). The other main objective was to assess the frequency of serious side effects, namely pulmonary edema, suspected raised intracranial pressure, and allergic reaction." (p. 1631)**

Methods: **Open-labeled randomized controlled trial from June 2006 thru December 2008 at the high dependency unit of Kilfi District Hospital in Kenya. Eligible patients were children >6 months old with severe malaria as defined by impaired consciousness (coma or prostration, Blantyre Coma Score ≤ 2) or respiratory distress in conjunction with plasmodium falciparum parasitemia and metabolic acidosis (base deficit >8). Exclusion criteria included Hg <5 g/dL, pulmonary edema (clinical evidence and O_2 sat <90%), established renal failure, congenital heart disease, severe malnutrition, or decompensated shock (SBP <70 mmHg if under age 1 or <80 mmHg if over age 1). Consent had to be obtained from parents prior to enrollment in this trial. Another trial comparing IV artesunate with quinine was conducted concurrently and children were enrolled in both studies simultaneously (AQUAMAT Controlled Trials Registration Number ISRCTN: 50258054).**

Children were randomized to receive 20cc/kg over one-hour of either Dextran or HES. At one-hour clinical assessment occurred and another 20cc/kg was administered if any of the following were not attained: appropriate heart range for age, cap refill <3 seconds, SBP ≥70 (<1 year old) or ≥ 80 (>1 year old), and oxygen sat >95%. Children received antimalarial therapy as per their randomization allocation in the AQUAMAT trial, but all other treatment protocols between groups were identical. Ventilation facilities were not available.

The primary outcome was the resolution of shock as defined by attaining resuscitation targets at eight-hours: absence of severe tachycardia (>180 if age <1 year, >160 if age 1-5, >140 if age ≥5 years), oxygen saturation <95%, cap refill ≥ 3 sec or SBP <70 (age <1) or <80 (age 1 year)

Secondary endpoints included in-hospital mortality, resolution of acidosis, volume resuscitation complications (pulmonary edema, raised intracranial pressure assessed clinically with NICU intracranial pressure monitoring), allergic reaction, neurologic sequelae at discharge and one month. Formal sample sizes were not calculated since

no preliminary data was available from which to estimate effect size. Investigators planned to recruit 40 children in each arm of the study and adverse events were reported to the local safety monitor and the national ethics board on a case-by-case basis.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Fluid interventions were randomly assigned using cards in pre-sealed opaque envelopes indicating either Dextran or HES by the admitting clinician. A separate randomization was used for the AQUAMAT trial. The randomization lists and envelopes for each trial were prepared separately and in advance of each trial by an independent person not involved in recruitment, and the lists were not available to the investigators. Randomization cards were numbered consecutively and opened in numerical order." (p.1632)
2.	Was randomization concealed (blinded)?	No. "The intervention arms were not masked in either trial." (p. 1632)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "The analyses were conducted by intention to treat." (p. 1632)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "…no statistically significant differences in the age or weight for the two intervention groups." "As an index of imbalance inherent within study groups in a small trial, we compared a priori risk factors by treatment arm and found very few differences. The exception was hypoglycemia, being slightly more common in children randomized to HES 12 (30%) compared to 5 (13%) receiving Dextran (p=0.09)." (p.1632)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	

1.	Were patients aware of group allocation?	Yes. "The intervention arms were not masked in either trial." (p. 1632) Therefore, potential for ascertainment bias.
2.	Were clinicians aware of group allocation?	Yes. "The intervention arms were not masked in either trial." (p. 1632). Therefore, potential for co-intervention bias.
3.	Were outcome assessors aware of group allocation?	Yes. "The intervention arms were not masked in either trial." (p. 1632) There is no logical reason why outcome assessors cannot be blinded in any trial. Failure to do so risks ascertainment bias.
4.	Was follow-up complete?	No lost to follow-up reported in text or CONSORT diagram (figure 1, p. 1632).
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 133 children screened for eligibility and 79 ultimately enrolled with median age 40 months (interquartile range 28-53 months) and 50% of cases presenting in deep coma, as well as 63% with one or more signs of impaired perfusion. • One child had streptococcus pneumonia bacteria and meningitis, but no other child had microbiological evidence of sepsis, UTI, or meningitis. (p. 1632) • **No statistically significant differences were found in the proportions attaining resuscitation targets between the two intervention arms at either 4- or 8-hours.** • Differences in secondary outcomes were noted with less HES patients (8%) suffering persistent acidosis at eight hours than Dextran patients (28%, p=0.05). This would equate to NNT=5 (95% CI 3-206). In addition, statistically insignificant decreased mortality noted in the HES group (5% vs. 11% in dextran arm). • No deaths between discharge and 1-month follow-up were observed. • No cases of pulmonary edema, elevated ICP, renal impairment, bleeding complications, or allergic reaction were observed. • Both Dextran and HES produced a decreased mean heart rate with time, but Dextran arm had higher post-intervention respiratory rate than HES.
2.	How precise was the estimate of the treatment effect?	No 95% CI's were reported which is particularly problematic in small underpowered trials.

III.	How can I apply the results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Dissimilar to developed world patients since immunization and nutrition status of Kenyan children likely suboptimal. Furthermore, the exposure to malaria (and drug-resistant malaria) in developing world is unlike what we will experience in the U.S. However, these patients are quite similar to the child in our vignette.
2.	Were all clinically important outcomes considered?	Yes. Mortality, clinical sepsis resolution, 1-month neuro outcomes. However, patient-centric outcomes (mortality, functional recovery) ought to be the primary outcome of these trials rather than disease-oriented outcomes like resolution of shock or resolution of acidosis.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain since no formal costs provided, however this evidence in conjunction with an ongoing RCT comparing albumin to saline (FEAST ISRCTN:69856593) "may lead to major policy changes" in developing world first line therapy (and funding) for severe malaria (and shock-states in general)
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	In Kenya as children with severe malaria, IV HES may be better therapy than Dextran to reduce death, although this is a small trial and we are unable to evaluate the margins of error. More research is coming but compared with Dextran, one needs to treat five severe malaria patients with HES to alleviate one case of acidosis at eight hours that otherwise would have persisted.

Limitations

1) **Failure to report which antimicrobial therapy (quinine vs. artesunate) each subject received. What if differences attributable to quinine or artesunate rather than HES or Dextran?**

2) **Lack of modeling to adjust for prognostic imbalances at study onset.**

3) **Failure to blind outcome assessors.**

4) **No 95% CI reported**

5) **Failure to reference or use CONSORT criteria.**

6) **No *a priori* sample size (ethics of under-powered trials) and failure to provide *post-hoc* power calculation.**

Bottom Line

In the developing world in severe pediatric malaria with impaired consciousness or respiratory distress, HES and Dextran are both safe for acute volume expansion therapy and no adverse outcomes observed among 80 patients. However, impressive trends observed favoring HES to reduce mortality and resolving acidosis at eight hours with NNT=5. Future studies should use CONSORT criteria and appropriate powering to better understand efficacy of these treatment options.