Author's response to reviews

Title: A prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis (protocol) The comparative rehydration in bronchiolitis study (CRIB)

Authors:

Ed Oakley (Ed.oakley@southernhealth.org.au)
Franz E Babl (franz.babl@rch.org.au)
Jason Acworth (Jason_Acworth@health.qld.gov.au)
Meredith Borland (Meredith.Borland@health.wa.gov.au)
David Krieser (David.Krieser@wh.org.au)
Jocelyn Neutze (Jocelyn_Neutze@middlemore.co.nz)
Theane Theophilos (theane.theophilos@mcri.edu.au)
Susan Donath (Susan.donath@mcri.edu.au)
Mike South (mike.south@rch.org.au)
Andrew Davidson (andrew.davidson@rch.org.au)

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Author's response to reviews: see over
Dear Mr Aulakh

Re: Protocol for the prospective randomised trial comparing nasogastric with intravenous hydration in children with bronchiolitis

The comparative rehydration in bronchiolitis study (CRIB)

MS: 1582445646340298

Thank you for the reviews comments and the opportunity to improve this manuscript. Below I outline our replies to the reviewers and the changes made to the manuscript.

Reviewer Joseph Zorc

1. The authors make no hypothesis of which therapy they expect to be superior, although they hypothesize that there will be a difference.
   - We hypothesise that there will be a difference in our primary outcome measure (length of inpatient stay) but do not know in favour of which intervention this will be (we have no data from our own experience or published studies to make an informed estimate of the direction and magnitude of the difference between the 2 treatments.). We have hypothesised that the trial will show one intervention better (i.e. not an equivalence trial) and have arranged the sample size and power calculation accordingly. The manuscript has not been altered in this regard.

2. On page 8 of the Methods (Sample size, power, and statistical methods) there are several areas where Pilot data on page 8 is referenced. I don't see this information in the manuscript and this should be clarified.
   - The references to the pilot data have been removed as the data referred to had already been placed in the manuscript at these points.

3. The justification for sample size is somewhat different from what is done in many trials.
   - A clinically important difference in length of inpatient stay of greater than or equal to 12 hours was predetermined for the trial and has been added to the manuscript at this point. The complication power was not the driver of sample size and is included to give some outline of the difference in complication rates the trial is able to assess.

4. A section on limitations has been added to the manuscript

Reviewer Federico Martinon-Torres

1. The exclusion of children < 2mo & why?
   - Young children were excluded as it was felt that this group have a different clinical course of bronchiolitis and are more likely to have severe symptoms. The cut off point was arbitrary and could have been reduced to 4 weeks but 8 weeks was our consensus. A description of this reason has been added to the manuscript.

2. The upper limit of 12 (instead of 6 or 24 mo, for example)
   - These patients were excluded because over this age other diagnoses – such as asthma – impact significantly on this group of patients. This has also been included in the manuscript.
3. I cannot understand the limit of 100% normal daily requirements...what if tachypneic, febrile, or just already dehydrated when admitted? How are you going to provide (and control) this extra needs then to the child?
   • Again this was a consensus position for a number of reasons – children with bronchiolitis often have SIADH and need less than maintenance fluid to maintain normal hydration. Children needing an IV bolus of fluid for resuscitation are excluded from the trial, removing all the significantly dehydrated patients. Our desire was to limit fluid overload by initially requesting this fluid rate. We do not control for other fluid requirements, these are up to the discretion of the managing paediatricians. We collect all this information as a protocol deviation, but do not control for fluid administration as it was thought to be too complicated and was unlikely to impact on our primary outcome measure. No change has been made to the manuscript regarding this point.

4. In page 6, the laboratory investigations: after reading it I have understood that this laboratory investigators will exclusively performed in those randomised in the IV fluid management group.
   • This is correct. This part of the protocol outlines current clinical standards of care in Australia and New Zealand only and does not mandate more intervention than this. Current practice is not to routinely collect electrolytes on NG hydrated patients. We surveyed staff regarding having blood tests done on all patients and realised this would have a major impact on ability to recruit patients so did not pursue this as it was not thought to impact on our primary outcome. The manuscript has been altered to show that this management is in line with current practice.

5. Re the clinical observation and record, why not using an already existing scale such modified Wood-Downes, or similar?
   • We did not use a scoring system as there is no score that has been clinically validated (and only the Respiratory Distress Assessment Instrument has been assessed for validity and reliability). This trial wanted to mirror current clinical practice which does not include the use of any scoring system. No change has been made to the manuscript regarding this issue.

6. There are some repetitions that may be omitted (page 6 first paragr and page 7 2nd parag). Please review the rest of the text
   • Repetitions have been removed

7. The use of any further medication nebulized or systemic should be protocolized or at least controlled!! Are you considering this
   • We do not control for medication usage, but do record this use and will report it in the trial publication. Use of ancillary medication is not frequent in Australia and New Zealand and the clinical practice guidelines regarding bronchiolitis management all recommend against use of these medications in the age groups included in the trial. This was added in the limitation section

8. Regarding subgroup analyses
   • No subgroup analysis has been calculated into the trial sample size. Any such analysis reported will be described and indicated as a post hoc analysis. Factoring in these subgroup analyses would have increased the sample size to a level unobtainable for our research network.

Sincerely

Ed Oakley
Principal Investigator CRIB study