Reviewer's report

Title: Racemic epinephrine during hospitalization improves acute respiratory distress but does not shorten length of stay for bronchiolitis: a randomized controlled clinical trial

Version: 1 Date: 21 January 2005

Reviewer: Hema Patel

Reviewer's report:

General

Thank you for the opportunity to review this paper. This is a well done controlled trial with care taken to ensure balanced randomization and to ensure double-blinding. It will be the third recent trial to evaluate extended-use epinephrine in admitted patients with acute viral bronchiolitis (refs 24 and 25 are two other RCTs). All 3 trials report similar results, with the other two having at least double the sample size of this trial. This paper will add valuable information to the field. I hope that the comments below are of use to the Editors and authors.

Comments below are listed according to section of paper:

1. title - major revision suggested see below
2. abstract- As I will discuss in results, the RDAI did not differ by 2 or more points between study groups except on day 1 (and with enrolment allowed up to 24 hours after admission this might include children who had received little if any study drug), so although results were at times statistically, mathematically significant, the clinical relevance of a less than two point difference is unclear. There is at least one study (Menon et al.) suggesting that a two point or greater difference implies clinical relevance. Without further supporting documentation on the relevance of this relatively small difference in mean RDAI scores, it is misleading to suggest that this infers respiratory benefit in one group over another. Add to this the inter-rater variability (not mentioned in the paper but there were two sites so presumably at least 2 and likely more than 2 raters)then this small difference between groups becomes even more difficult to interpret.

As an aside, we are missing a robust measurement tool for infants with viral bronchiolitis. It is true that the RDAI has been used frequently (and in fact in one of our own trials - reference 24) however, in researching the score, it is clear that it is not an ideal primary outcome. There is inter and intra rater variability and some of the measurement items are not clear (for example wheezing in different parts of the respiratory phase, location in "4 lung fields" (never actually defined by Lowell et al.)) Length of hospital stay is a clinically relevant outcome measure as are items such as duration of poor feeding, duration of supportive fluids, duration of supplemental oxygen. Many of these outcomes were included appropriately but the study was powered for a 4 point difference in RDAI (day 3).

The limitations of the primary outcome measure (RDAI) must be discussed.

Background - appropriate

Methods- How was "feeding pattern" operationalized for the purposes of the study? How were breastfed infants assessed? Were there supporting body weights, urine specific gravity? Who reported this measure and how was it validated?

Results:

How many children were eligible to enroll in the trial? How many were from IWK and how many from
the NB site? How many were not enrolled and for what reasons? This is important to understand whether there was selection bias and for interpretation of the generalizability of the findings. A flow diagram (CONSORT style) would be helpful.

How many research nurses measured the RDAI in study children? Were inter-rater reliability checks performed? What were the results? (very important as there are two sites, at least two people involved and the RDAI is variable between raters)

What was the availability of the research nurse? If enrolment could occur up to 24 hours after admission and we see that most children were only hospitalised for 1-3 days, then it may be that a substantial portion of children were exposed to the intervention for a brief period of time. Example, child comes to ED at 8 pm gets treated according to standard care until 9 am next day and then gets enrolled and then goes home at 5 pm.

The authors should verify and summarize:
1. # of study doses received per group, per site
2. duration enrolled in trial per group, per site

Was there a difference in results by study site? This is not mentioned or discussed in the paper. Must be included.

Was there any contamination? If so, what was the magnitude?

Page 10, line 17 - please clarify what the comparison values represent
Table 2 - baseline characteristics - should this table include p-values, CONSORT guidelines suggest not to include as with randomization should be fairly equal, for the authors to review and discuss
Figure1 - quite a wide variability in feeding by day both within and between groups, expected to see some discussion of these findings in discussion section. The legend is incorrect (minor R instead of RE) and there is one type of fill-in not included (plain white, white with little dots, black with white lines and all black) but only 3 categories in the legend. So I am not sure what the results actually are. And because I am not sure how the feeding outcome was operationalized, I am not sure how to interpret the graph as is.

Discussion:
This is the third study (refs 24 and 25 are other two) looking at extended use epinephrine in similar (but not identical populations). There is a good meta-analysis on overall epi use in this population (Hartling reference). It would be useful to look at the similarities/differences between this trial and the other two. Results were not so different and yet the interpretation of similar results is different - why? This type of discussion would be more relevant than the more didactic discussion of why there may have been a mathematically significant improvement in the epinephrine treated group.

Clinical relevance of the findings must be addressed, particularly with the known limitations of the RDAI and the known difficulties in measuring respiratory distress in this patient group. By its very nature, bronchiolitis is an variable condition, although it has a prodrome, peaks at 3-5 days and lasts approximately 14-21 days, there are ups and downs in the infant's respiratory distress throughout this period that need to be taken into consideration.

Please note that Wainwright also studied extended use in hospital, with aerosols Q4h for the duration of the hospitalisation. This needs to be corrected in the discussion.

If the feeding was as variable as it appears it was (getting worse on day 2 in one group?) then there needs to be some discussion of results, particularly as they were felt to be important enough to include in a diagram.

Overall, I think it will be very important to put the magnitude of the differences found in RDAI into a realistic perspective for the reader. Although sparse, the available literature does not support a
clinical relevance to differences of less than 2. (Indeed the authors powered their study to look for a difference of 4 - why did they choose this value? Was it for sample size or did they think that this would be a truly important group difference? If the latter is true then this should be discussed and the perspective of the results should reflect a statistical but not clinically relevant difference.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

I believe that the title is misleading (see more detailed comments under minor revisions) and should be shortened to:
Racemic epinephrine compared to salbutamol in hospitalised young children with bronchiolitis: a randomized controlled clinical trial

Given the multiple comparisons, need for evaluation of results by site, I think it would be reasonable for a statistician to review the manuscript.

The comments described above under general comments fall under revisions that I am expecting the authors to address.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes

Declaration of competing interests:

I too am a researcher in the field of acute viral bronchiolitis. I am currently a co-investigator in a large multi-centre study evaluating the use of short-term epinephrine and high dose oral dexamethasone in infants with viral bronchiolitis.

I am a co-author of a Cochrane meta-analysis on the effectiveness of epinephrine in this patient group.

I have no competing financial interests.