Author's response to reviews

Title: Computerized acoustic assessment of treatment efficacy in RSV Bronchiolitis: Nebulized Epinephrine Versus Albuterol- a double-blind study.

Authors:

Raphael Beck (r_beck@rambam.health.gov.il)
Nael Elias (n_elias@rambam.health.gov.il)
Shay Shoval (shoval@hotmail.com)
Tov Naveh (mdnave@tx.technion.ac.il)
Gil Talmon (g_talmon@rambam.health.gov.il)
Simon Godfrey (sgodfrey@netvision.net.il)
Lea Bentur (l_bentur@rambam.health.gov.il)

Version: 2 Date: 14 September 2006

Author's response to reviews: see over
Point-by-point response

Manuscript #: 1287293261034939

Original manuscript title: Computerized acoustic assessment of treatment efficacy in RSV bronchiolitis: nebulized epinephrine versus albuterol – a double-blind study.

Current manuscript title: Computerized acoustic assessment of treatment efficacy of nebulized epinephrine and albuterol in RSV bronchiolitis.

Authors: Raphael Beck, Nael Elias, Shay Shoval, Tov Naveh, Gil Talmon, Simon Godfrey, Lea Bentur.

Referee 1

Major points

1. We have revised both the introduction (last paragraph) and the discussion (first and last paragraphs), to further clarify that the study primarily evaluated the use and feasibility of lung sounds analysis in infants with RSV, and that the response to nebulized albuterol vs. epinephrine was a secondary outcome. Bisgaard studied asthmatic children, whereas our subjects had RSV-positive bronchiolitis. Tal et al., in another study utilizing lung sounds analysis in young children with bronchiolitis (24), had a population size of 16 children. In light of the Reviewer’s comment, the limitation of the small sample size in our study has been added to the discussion.

2. The PulmoTrac system for computerized lung sounds analysis and wheeze detection/quantification has been described in detail in a number of previous
publications by our group (ref. 25 in the current manuscript and 1-3 at the end of this response), as well as presented in a number of published abstracts in international conferences (4-7). We therefore thought it would be superfluous to repeat it in great detail, as this is a short report on a pilot study. The subject of computerized lung sounds analysis has been described and discussed in the literature previously, as there are a number of groups in Canada, the U.S.A and Europe working on this application. International consensus guidelines (8) and a definitive textbook (9) have also been published. According to the reviewer’s suggestion, we added more information on the utility and shortcomings of computerized lung sounds analysis in the clinical setting to both the introduction and the discussion. The first sentence of the conclusion has been changed to better reflect the result of this study.

3. The clarifications regarding nebulized treatments and recording technique have been added to the Methods section. A table outlining the clinical score has been added (Table 1), including a reference. The definition of poor feeding has been added to the Legend of Table 2.

4. The patients with a higher clinical score tended to have higher wheeze or crackle counts, but it did not reach statistical significance. This has been added to the Results.

Minor points

1. The title was changed – “double-blind study” omitted.

2. The abstract was revised and the sentence was removed.

3. The description of the study design was corrected accordingly.
4. The sentence was corrected

5. The terms were changed to “Epinephrine” and “Albuterol”. There were no dropouts; however, the results were provided as Yes/No, which was not clarified. This has now been changed, and only the “yes” numbers appear.

6. The statistics were done again. The mean clinical score in the Albuterol group is higher, but not statistically significant from the Epinephrine group. In theory, the increase in wheeze rate can be explained by improved flow rates post-albuterol, creating more wheezes; however, because of the large variability (high SD), this did not reach statistical significance.

References


**Reviewer 2**

**Minor Revisions**

1. These results were moved, as suggested, to the Results section.
2. The Introduction has been revised to reflect the main aim of the study, i.e., test the feasibility and accuracy of conducting lung sounds analysis with wheeze and crackle quantification on these babies.

3. We used l-epinephrine. This has been added to the manuscript, as well as the nebulizer details.

4. The same investigator assessed all patients. This has been added.

5. Crackle count refers to number of crackles per breath – this has been added in the Methods section.

6. Heart and respiratory rate scores have been added to Table 3. Although one might expect increase in HR with epinephrine compared to albuterol, HR also increases with work of breathing. In our study, we found no significant difference at 10 minutes, whereas HR decreased in the epinephrine group after 30 minutes, which may reflect some clinical improvement.

7. The discussion has been revised to reflect and address these issues.

8. We apologize for the mishap. The correct Figure 3 is now included.

Reviewer 3

Major points

1. The statement at the end of the introduction was revised to better clarify the aim of the study, similar to the one under "aim" in the Summary. In addition, the whole introduction was revised to better reflect the aim of this study, i.e., test the feasibility and accuracy of computerized wheeze and crackle quantification, rather than the effect of the treatments.
2. Since this was a pilot study intended mainly to test the feasibility and accuracy of automatic wheeze and crackle quantification in a population of very young infants, but not intended to replace the clinical score, and with response to treatment being secondary, a power calculation was not done. Based on the earlier study by Tal (5), who studied 16 subjects with significant results, we aimed for approximately double that number. Twenty-seven infants were recruited before the RSV season ended. All clinical observations were performed by a single observer (SS), to eliminate inter-observer variability. The setting of bronchiolitis was chosen for two reasons: a. according to Tal's study (24), we expected to find changes in wheezes and/or crackles in response to the treatment and even between the two treatments, as per Sanchez et al (5). b. test the system in a difficult and uncooperative population of babies, who are ill, in respiratory distress and often irritable. We chose to compare the clinical score to the PulmoTrac as more clinically appropriate than having the clinician try to quantify crackles or wheezes with a stethoscope and compare this to the PulmoTrac findings. During the off-line auditory audit of the data there was agreement between clinician and PulmoTrac results in all sound segments which were analyzed. As now stated in the discussion, a larger study is needed to study the clinician vs. PulmoTrac assessments of response to treatment.

Minor Points

1. Table 1 has been added to detail the clinical score and a reference added (12). The term “Dyspnea” was used to describe retractions and has been changed.
2. Sampling frequency and bit rate have been added in the Methods section. Crackle characterization, detection and validation methods were also added to the Methods, including references.

3. The details regarding patient numbers have been added to the Results section.

4. The adhesive pad with which the sensors were applied to the skin provided sound shielding. Environmental noise such as speech, ringing, beeps, bumps etc, were identified with an external microphone near the patient and electronically removed from the recording data. Occasional motion artifact and the baby’s own crying interfered with the recording. These did not interfere with the automatic wheeze and crackle detection, as the algorithm did not identify them as “events” and “ignored” them. It usually took 4-6 hours per patient to edit and analyze the data.

5. Crackle count refers to number of crackles per breath – this has been added in the Methods section.

6. The results in Table 2 were provided as Yes/No, which was not clarified. This has now been changed, and only the “yes” numbers appear.

7. We apologize for the mishap. The correct Figure 3 is now included.

**Discretionary Revisions**

Discussion of low wheeze counts compared to Tal’s study has been added.

**Editorial changes**

1. Informed consent is now documented – Results section, first paragraph.
2. Competing interests section has been added.

3. Authors contribution section has been added.

4. Acknowledgement section has been added.

5. Trial registration number has been added: ClinicalTrials.gov # NCT00361452.

6. The references have been reformatted according to BCM Pediatrics requirements.