Author’s response to reviews

Title: The use of an alternate side lying positioning strategy during inhalation therapy does not prolong nebulisation time in adults with Cystic Fibrosis: a randomised crossover trial

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BMC Pulmonary Medicine

Please respond to the reviewers comments point-by-point and incorporate your responses in to a revised version of your manuscript.

Reviewer reports:

Stephen Bourke (Reviewer 1): This is a well conducted study with a clear description of the methodology and results. Appropriate Ethics Committee approval is clearly stated. However the study is very limited in its nature and goals as it is confined simply to demonstrating that nebulisation time is the same when the patient uses an 'alternate side lying position' versus an 'upright position' when nebulising saline. The study design did not include any other significant outcomes such as lung deposition of the inhaled agent, or upper lobe versus lower lobe
deposition. It therefore provides only preliminary information on the potential role of nebulising posture in the clinical treatment of patients with cystic fibrosis. It is therefore of limited relevance, at this stage, to clinical practice.

Response: We thank Stephen Bourke for taking time to review our paper. We agree this is preliminary information that has informed the methodology of a subsequent trial. This study confirms the alternate side lying strategy is practical in that it does not prolong nebulisation time. Three additional research questions are addressed in a subsequent study:

1. What is the impact of side lying on the proportion of the dose loaded in the nebuliser that is deposited in the lungs?

2. What is the impact of side lying on the uniformity of deposition throughout the lungs?

3. What is the impact of side lying on the apical drug density as a percentage of the drug density in the remaining lung?

Malcolm Brodlie (Reviewer 2): I enjoyed reading this well-written manuscript.

Although a relatively simple study design it is carefully described and executed.

Importantly the research question is one that is relevant to people with CF and clinicians.

It is acknowledged that the study is not definitive/comprehensive enough to support a change in clinical practice but is likely to prompt further research in this area.

Response: You are correct. See response above.

My specific comments are:

- Were participants not asked about their experiences of the 2 different techniques for nebuliser delivery? Why were PROMs or narrative-style experiential data not collected? This could be worthy of discussion.
Response: We did not collect this data in this small preliminary study. However, we do raise the issue in two other publications. A concurrent inpatient trial by our group, now published in Thorax, raised the issue and reported that many participants preferred side lying for inhalation for comfort and convenience but there was no data at that time to suggest deposition would be equivalent and no data about the effect on nebulisation duration. In the subsequent trial mentioned above we again ask participants regarding their preference.

- Abstract: in the results section correlations are mentioned with height, lung function and delivery time ... I could not find details of these in the main body of the paper

Response: We apologise that the relevant paragraph was omitted. The final paragraph in the Results section now presents this information.

Correlations

There was no significant correlation between delivery time and any of the following parameters in either position: FEV1, FVC, FEV1 % pred, FVC % pred, or participant height (all R2 <0.4).

- Introduction: as a minor point can you confirm that this subject has never been examined previously, ?not even in in vivo/experimental models where drug deposition could be more easily studied

Response: This is the first study to investigate this subject. This was stated in the first paragraph of the Discussion section. We have moved this text to the end of the Background section.

- Methods: Aim 2: could be rephrased there are too many 'cans' as written

Response: We agree and have reworded this as suggested.

- Was data recorded about the natural decay in rate of delivery that occurs with normal saline in this nebuliser? It is alluded to in the text a couple of times but not demonstrated that I can see ?could be supplementary information
Response: We have mentioned the decay after 10 minutes in the third paragraph of the Background section, citing a published abstract in which the LC-Star was used to deliver rhDNase. In pilot data generated to guide the design of the submitted study, we confirmed the same deterioration in the delivery rate of normal saline by the LC-Star. We now include these pilot data as an electronic Appendix to the paper.

- Along the same lines, linked to the comment above, worth stating how long this type of nebuliser takes for delivery of a 'typical' CF medication, the durations seem quite long compared to some other systems to this reviewer

We have included a paragraph near the start of the Discussion section, stating that the duration of delivery is consistent with the product information and with previous work from our centre. This paragraph also explains why clinicians may often observe a faster delivery time for 4mL of normal saline when patients only nebulise until the first sign of intermittent delivery, rather than continuing until the dead volume has been reached.

We have also added text near the end of the Discussion section, stating the need for future work to consider the impact of faster delivery systems and additional inhaled therapies (dornase alfa, antibiotics) with differing viscosities.

- Discussion: I agree people with CF might choose to alternate sides between nebuliser sessions but think could be worded slightly more strongly that it hasn't been investigated specifically in this study in terms of looking at alternate sides or drug deposition, may be suboptimal clinically depending on the mechanism of action of the particular drug if only delivered effectively every 48 hours for example if od regime

Response: We agree and have amended the wording near the end of the Discussion section to make this point more forcefully.

- Legend for fig: would be nice to see the associated CIs and stats included in the legend so it can stand alone

Response: we have updated the figure as suggested
- Supplementary info says copyright Respiratory Research: needs to be changed and could you confirm not previously published in Respiratory Research?

Response: Thank you. We have corrected this and confirm it has not previously been published