

## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Nasal high-frequency oscillatory ventilation (nHFOV) versus nasal continuous positive airway pressure (NCPAP) as an initial therapy for respiratory distress syndrome (RDS) in preterm and near term infants
<b>AUTHORS</b>	Iranpour, Ramin; Armanian, Amir-Mohammad; Abedi, Ahmad-Reza; Farajzadegan, Ziba

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting USA Competing interests: None
<b>REVIEW RETURNED</b>	19-Jan-2019

<b>GENERAL COMMENTS</b>	<p>I mostly confine my remarks to statistical aspects of this paper.</p> <p>One non-statistical point: The title includes the word "preterm" but this is not defined and the exclusion criteria exclude preterm babies</p> <p>I have a number of concerns that need to be addressed before I can recommend publication.</p> <p>p 2 line 34-5 Either "shorter" or "significantly shorter", there is no such thing as "statistically shorter"</p> <p>p 8 - Even though the babies were randomized, it would be a good idea to include relevant covariates and do the appropriate sort of regression for each outcome. This can lead to more powerful tests.</p> <p>Variables cannot be parametric or non-parametric, only models can. Do the authors mean normally distributed?</p> <p>p values are not relevant in table 1 or 2, the key is how big the differences are, not whether they are significant, so delete phrases on line 38-8 and 51</p> <p>For the dichotomous variables, what method was used? A t-test of proportions? (I would suggest logistic regression).</p> <p>Tables 1 and 2 - delete the p value column</p> <p>Table 2 - there do seem to be some fairly large differences in a) Number of surfactants received and steroids; also, HCO<sub>3</sub> and PH were similar in the two groups, but the variability in the two groups was very different.</p> <p>Table 3 - was any adjustment made for multiple comparisons?</p>
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	If so, which one? If not, why not? (one can argue that none is needed but the authors should state that.)
<b>REVIEWER</b>	Reviewer name: Yuan Shi Institution and Country: Chongqing Medical University affiliated Children's Hospital, Chongqing 400014, China. Competing interests: None
<b>REVIEW RETURNED</b>	07-Feb-2019
<b>GENERAL COMMENTS</b>	Major concern: 1.NHFV should be nHFOV,because the authors stated they use only the ventilator of nHFOV mode. 2. The major outcome is "Duration of non-invasive support", but there is a problem on it. In nHFOV group, there was no intubation, but in nCPAP group, there were some patients with intubation, which was a interfere factor for this index. 3. The gestational age <30 wks should be research focus. Minor questions: 1. "Introduction Line 27-30" 43-80% of infants with moderate to severe respiratory failure who are initially treated with nasal CPAP need mechanical ventilation [10]. Is that correct? The ventilation rate is too higher as compared with other reports. 2."Intervention Line 41" 20mmHg should be 20cmH2O?!

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I mostly confine my remarks to statistical aspects of this paper.

One non-statistical point: The title includes the word "preterm" but this is not defined and the exclusion criteria exclude preterm babies

I have a number of concerns that need to be addressed before I can recommend publication.

p 2 line 34-5 Either "shorter" or "significantly shorter", there is no such thing as "statistically shorter"

Reply: Thank you, it was corrected.

p 8 - Even though the babies were randomized, it would be a good idea to include relevant covariates and do the appropriate sort of regression for each outcome. This can lead to more powerful tests.

Reply: With respect to your comment; we revised the statistical analysis subsection in methods section; and as can be seen we used another statistical tests for comparing the continuous and categorical data between two study groups; and as you declared the covariates are not significant even at  $p < 0.2$  that we could enter then in multivariable analysis on the other hand as an important point our sample size does not permit to enter more variables in the model; also please note our objectives are to compare the variable between two groups not association analysis that can be captured by regression analysis;

Variables cannot be parametric or non-parametric, only models can. Do the authors mean normally distributed?

Reply: Thank you very much for your valuable point; we revised the statistical analysis subsection extensively and focused particularly on your proposed comments. Please see statistical analysis subsection.

p values are not relevant in table 1 or 2, the key is how big the differences are, not whether they are significant, so delete phrases on line 38-8 and 51

Reply: you are right; some variables have relatively large differences between groups; however, we should rely on appropriate statistical tests and we revised some variables presentations and statistical test for them based on your comment; we know your mean that statistically significant is different from clinically significant; however, in table 1 and table 2 we compared baseline demographic and clinical characteristics of study participants. In current version we used term "comparable" instead of not significant in some sections. Some experts in RCT suggest that it is not needed to do statistical tests for comparing baseline variables between groups; however, majority of expert in RCT field such as Friedman et.al. (Fundamentals of clinical trials; fifth edition) suggest strongly to do statistical analysis after randomization; please see chapter 9 (baseline assessment; last subsection: testing for baseline imbalance).

For the dichotomous variables, what method was used? A t-test of proportions? (I would suggest logistic regression).

Reply: Thank you for your comment; we revised statistical analysis subsection and present the chi-square or Fisher exact tests for comparing categorical data between two groups and appropriately footnoted the used tests at the bottom of tables; we used chi-square or fisher exact tests for evaluating the differences between two groups; logistic regression is applicable for association analysis.

Tables 1 and 2 - delete the p value column

Reply: Please see our reply to your above comment regarding to doing statistical test for baseline values; if you are agreed; we do not delete the p-values. Please see chapter 9 book: Fundamentals of clinical trials by Friedman et.al fifth edition

Table 2 - there do seem to be some fairly large differences in a) Number of surfactants received and steroids; also, HCO3 and PH werre similar in the two groups, but the variability in the two groups was very different.

Reply: Many thanks for your comment; we present the used non-parametric statistical test i.e. Mann-Whitney U test and due to their non-normality of the mentioned variables we presented in current version median (inter quartile range: IQR) beside of mean (SD); please see table 2 and table 3 its footnotes.

Table 3 - was any adjustment made for multiple comparisons? If so, which one? If not, why not? (one can argue that none is needed but the authors should state that.)

Reply: many tanks; we footnoted that the p-value are based on Bonferroni correction for multiple testing.

Reviewer: 2

Major concern:

1.NHFV shoud be nHFOV,because the authors stated they use only the ventilator of nHFOV mode.

Reply: Thank you, it was corrected.

2. The major outcome is "Duration of non-invasive support", but there is a problem on it. In nHFOV group, there was no intubation, but in nCPAP group, there were some patients with intubation, which was a interfere factor for this index.

Reply: As we wrote in the methodology "Duration of non-invasive support" was primary outcome but we considered some secondary outcomes such as treatment failure. Treatment failure means need to ventilator or need to intubation in both groups. Need to intubation was a secondary outcome and significantly was less in nHFOV group. Results did not indicate that increased need for intubation in NCPAP group led to decrease in "Duration of non-invasive support". On the contrary, with increasing intubation in NCPAP group, the duration of non-invasive support in nHFOV decreased. Thus, this was not effect on primary outcome.

3. The gestational age <30 wks should be research focus.

Reply: I very much agree with you. As you know studies on nHFOV are very limited. We had some limitation with the ethics committee. We must first prove the safety of this method as an initial mode in premature neonate (but not very premature) and then in future studies certainly we will focus on preterm less than 30 weeks. Anyway studies in this method of treatment is very limited and this is not even a meta-analyze in this case even in premature neonate more than 30 weeks.

Minor questions:

1. "Introduction Line 27-30" 43-80% of infants with

moderate to severe respiratory failure who are initially treated with nasal CPAP need

mechanical ventilation [10]. Is that correct? The ventilation rate is too higher as compared with other reports.

Reply: I checked the relevant reference. Exactly this sentence was mentioned.

2. "Intervention Line 41" 20mmHg should be 20cmH<sub>2</sub>O?!

Reply: Thank you, it was corrected.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting, USA Competing interests: None
<b>REVIEW RETURNED</b>	11-Mar-2019

<b>GENERAL COMMENTS</b>	<p>I confine my remarks to statistical aspects of this paper. The basic methods are OK (although a better one is available) but I have some issues to address before I can recommend publication.</p> <p>General: Why do a t-test? it's not wrong, that is, it doesn't violate any rules, but a regression would be more illuminating and more powerful.</p> <p>Abstract: what are the numbers after the +- signs? SD? SE? CI?</p> <p>The title is "preterm" infants but on p 5 it says &gt; 30 weeks gestation. Do you mean &lt; 30 weeks?</p> <p>p 7 The formula could be better written and is missing a ). E.g. write a subscript for each z indicating alpha (for z 1) and beta (for z2).</p>
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	<p>The sentence explaining the formula needs to be rewritten.</p> <p>p 8 Why were non-normal variables transformed and why log in particular? Variables should be transformed for substantive reasons, not statistical ones.</p> <p>p 8 and table 1 and 2 - p values are not useful here. Delete that column from the table and delete those references from the text and consider the actual size of the differences in substantive terms.</p>
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## VERSION 2 – AUTHOR RESPONSE

I confine my remarks to statistical aspects of this paper. The basic methods are OK (although a better one is available) but I have some issues to address before I can recommend publication.

General: Why do a t-test? it's not wrong, that is, it doesn't violate any rules, but a regression would be more illuminating and more powerful.

Reply: We respected the reviewer and we did a linear regression analysis for significant continuous outcomes in table 3 and presented the results in results section; we also mentioned relevant matters about regression analysis in statistical analysis subsection in methods section. please see statistical analysis subsection as well as results section in current revised version of our manuscript.

Abstract: what are the numbers after the +- signs? SD? SE? CI?

Reply: Many thanks; we declare the presented results that are mean (SD), please note we presented continuous data as mean (SD) or median (IQR).

The title is "preterm" infants but on p 5 it says > 30 weeks gestation. Do you mean < 30 weeks?

Reply: The "premature neonates" in neonatal medicine refer to infants born less than 38 weeks. In this study we selected premature neonates but preterm neonates with gestational age of more than 30 weeks and less than 38 weeks. nHFOV was a very new method for treatment of premature infant with RDS as an initial therapy. So the ethics committee did not allow us to use it on very premature infant. For this reason, we decided to first apply this method to premature neonates who are more than 30 weeks. Therefore, all neonates in our study were premature and had a gestational age of over 30 weeks but less than 38 weeks. For better clarity, on page 5 and page 8, the "preterm neonates with gestational age between 30 and 38 weeks" replaced by " newborns with >30 weeks gestational age"

p 7 The formula could be better written and is missing a ). E.g. write a subscript for each z indicating alpha (for  $z_1$ ) and beta (for  $z_2$ ). The sentence explaining the formula needs to be rewritten.

Reply: Thanks; we revised the proposed sentence.

p 8 Why were non-normal variables transformed and why log in particular? Variables should be transformed for substantive reasons, not statistical ones.

Reply: Thank you, we clarify that the right skewed data were subjected to logarithmic transformation.

p 8 and table 1 and 2 - p values are not useful here. Delete that column from the table and delete those references from the text and consider the actual size of the differences in substantive terms.

Reply: we respected the reviewer and his comments and deleted the p-values and revise the sentence explaining the content of tables 1 and 2. Please see tables 1&2 in current version.