Peer Review File

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Reviewer comments: first round

Comment 1: The introduction section is too long and could be shortened (lines 9-11 on page 5 and lines 1-6 on page 6 could be cut).

Reply 1: We apologize that the introduction is too long. We have followed your advice and removed the sections you pointed out.

Changes in the text:

"In mechanically ventilated patients, mucociliary transport and coughing, the primary mechanisms for clearance of secretions, are impaired (1). In addition, artificial airways, inadequate humidification, and immobility can result in the accumulation of secretions, leading to ventilation/perfusion mismatch and increased work of breathing, which subsequently lead to a cycle of secretion increase (1). A previous study reported that atelectasis was found in 14% of mechanically ventilated trauma patients (2). Accordingly, the management of airway secretions is a critical issue, and mucoactive agents are often prescribed as part of the management of airway secretions.

In a survey of critically ill patients in the United Kingdom, 41% of mechanically ventilated patients received at least one mucoactive agent (3). Mucoactive agents include expectorants, mucolytics, mucoregulatory, and mucokinetic drugs, which are intended to increase the ability to expectorate secretions or reduce mucus hypersecretion (4). In a randomized controlled trial (RCT) on mechanically ventilated patients, on-demand compared with routine nebulization of NAC with salbutamol did not result in fewer ventilator-free days (VFDs) (5). In another RCT (6), intravenous NAC was administered early after admission in ventilated patients with acute respiratory failure, resulting in a shorter duration of ventilation. However, these studies had small sample sizes, and there was high heterogeneity; consequently, a meta-analysis concluded that the existing evidence was of low quality (7). To date, thus, the benefits of early or routine administration of mucoactive agents in ventilated patients are inconclusive." (see Page 5, lines 5-18, and page 6, lines 1-6)

Comment 2: The inclusion criteria and baseline variables measured are appropriate as well as the primary outcome (VFDs could be worded as " Days alive and free of mechanical ventilation in the first 28 days from intubation" replacing line 6 on page 9, and likewise for ICU-free days on line 16-17 on page 9). The selection of within 3 days although arbitrary seems appropriate in identifying/enriching patients at risk of prolonged mechanical ventilation.

Reply 2: Thank you for your suggestion. We followed your advice and revised the manuscript as follows.

Changes in the text:

"Our primary outcome was VFDs during the first 28 days of ICU stay. We defined VFDs

as days alive and free of mechanical ventilation in the first 28 days from intubation." (see Page 8, line 15-17)

"We defined ICU-free days as days alive and free of ICU admission in the first 28 days from intubation." (see Page 9, lines 8-9)

Comment 3: The results should include if possible the number of patients in the on-demand mucoactive arm who did receive any mucoactive agents during invasive mechanical ventilation.

Reply 3: Thank you for this intriguing suggestion. Of the patients in the on-demand group, 6 received mucoactive agents during ICU stay and 31 during hospitalization. Due to a lack of such data, however, we could not ascertain whether the on-demand group received invasive mechanical ventilation on the day the mucoactive agents were prescribed. If we included only patients who received mucoactive agents in the on-demand group, it would make a comparison of early and late administration of mucoactive agents, which is a new clinical question and accordingly a different study. In addition, because the population in the on-demand group differs from that in the primary analysis, the propensity score would have to be recalculated and the balance between groups may not be created. We therefore decided not to do the suggested analysis. We added the following sentence to the Results section.

Changes in the text: "Of the patients in the on-demand mucoactive agent group, six received mucoactive agents during their ICU stay and 31 received them during their hospitalization." (Page 11, lines 17-19.)

Comment 4: It would also be useful to have a distribution graph of VFDs in both the early mucoactive and on-demand mucoactive groups.

Reply 4: In accordance with your suggestion, we have made the figure of a distribution graph of VFDs in both the early mucoactive and on-demand mucoactive groups. The graph has been added as Figure 2. We have inserted the following sentence to the Results section.

Changes in the text: "Figure 2. shows the number of ventilator-free days for the early mucoactive agent group and the on-demand mucoactive agent group." (see page11, lines 12-14.)

Comment 5: The discussion needs to be reorganised in a more structured manner to be fit for publication. I suggest the authors refer to this paper by Michael Docherty (DOI: 10.1136/bmj.318.7193.1224; PMID:10231230) and structure the discussion accordingly.

Reply 5: Thank you for your helpful and educational advice. Based on the five structures presented by Docherty's article, we have reviewed and modified the structure of our discussion as follows:

1. statement of principal findings: we added the following sentence at the beginning of the discussion section.

"In this propensity analysis, we examined the association between early administration of mucoactive agents and VFDs in critically ill patients." (see Page 12, lines 11-12)

2. Strengths and weaknesses of the study: we have described them on pages 14 and 15. To make the description more explicit, however, we have added the following text: "There are several strengths to this study." (see Page.14, line3)

3. Strengths and weaknesses in relation to other studies, discussing particularly any differences in results: we have described the strengths compared to previous studies in the discussion section (see Page 14, lines 3-8.)

4. Meaning of the study: possible mechanisms and implications for clinicians or policymakers: we have described the mechanism by which mucoactive agents respond on page 12, lines 16-18. We have discussed the possible mechanisms by which mucoactive agents failed to ameliorate VFD on page 13, lines 10-13. We mentioned implications for clinicians on page 14, lines 8-17.

5. Unanswered questions and future research; On page 14, lines 14-18, we have mentioned the issues that require further studies in the future.

Reviewer comments: second round

Comment 1: Lines 235-243 (Paragraph 3 of discussion) should be replaced with
"There are several strengths to this study. To our knowledge, this is the first study to compare an early vs on-demand use of mucoactive agents in mechanically ventilated patients. Previous studies mainly compared mucoactive agents vs placebo with a meta-analysis showing no difference in mortality or duration of mechanical ventilation but an improvement in ICU length of stay. Our study used a clinically relevant endpoint of ventilator-free days and used propensity matching to reduce the risk of confounding in this non-randomised study. Especially given the heterogeneity of patients included in our study."

The authors cannot claim their study is larger than those included in the meta-analysis by Anand et. al. as some of the studies (Bandeshe 2016 and Van Meenen 2018) were larger than this study.
Reply 1: We apologize for the inadequate description of our study in the Discussion section. We have replaced the paragraph as you suggested.
(see page 15, line 3-10.)

Comment 2: Lines 243-251 (Sentence beginning "Oral or injectable...") should be moved below 278 to form its own paragraph.
Reply 2: Thank you for your suggestion. We followed your advice and moved the relevant sentence to the end of the discussion and made it an own paragraph. (see page 17, line 3-10.)