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Response letter

10th January 2016

Dear Shui Qiu,

thank you very much for accepting our paper entitled '*Efficacy of prone position in ARDS patients: A pathophysiology-based review*' (Manuscript NO.: 23523) for publication in your esteemed journal. We would like to express our gratitude for all the valuable and constructive comments we have received from the Reviewers and the Editor.

We have carefully revised our manuscript according to the peer-reviewers' comments, and the revisions have been highlighted using the Track Changes function:

- **Peer-reviewer's comment:** '*The background of the review is too much, and the author talk a lot of ARDS mechanical ventilation, it seems not relevant with prone ventilation*' - According to comment, we have shortened the introductory part to include only relevant background information.
- **Peer-reviewer's comment:** '*Conclusion suggests early and sufficient duration could improve outcomes of ARDS patients, however, the review does not show the timing and the optimal duration of prone position*' AND '*...to compare confounding variables such as ideal prone duration...*' - According to comment, the following text has been added: 'Clinicians intending to use prone positioning therapy face

the question of optimal duration of prone positioning sessions, which still remains controversial. Early studies were characterized by short prone positioning session of no more than 10 hours, ranging between 1-10 hours in the majority of the patients^[75,76,134]. Later studies used prolonged session of prone positioning, usually more than 12 hours ^[23,72-75,137,139] showing better results on mortality or morbidity but the majority of them did not achieve statistical significance. In their meta-analysis, Beitler et al^[134] stratified analysis by high (≥ 12 h/day) or low (< 12 h/day) proning dose and demonstrated a significant reduction in mortality with high doses (RR = 0.71; 95 % CI 0.56–0.90; $p = 0.004$) but not low doses (RR = 1.05; 95 % CI 0.92–1.19; $p = 0.472$)^[134]. Lee et al^[137] showed a negative trend for overall mortality when the actual duration of prone positioning was longer, but the effect of the duration of prone positioning on mortality did not achieve statistical significance (regression coefficient -0.037 ; 95% CI, -0.089 to 0.013 ; $p = 0.130$)^[137]. Thus, although data regarding optimal exact duration of prone positioning is far from being sufficient, it seems that periods of more than 12 hours of prone positioning are needed in order to improve outcome. According to our experience and the findings of the PROSEVA study, prolonged duration of proning even more than 24-36 hours, or a protocol of short period (i.e 1-2 hours) of supine positioning for daily nursing care between 24-hour prone sessions for 3-5 days are safe and seems to improve outcome in patients with severe ARDS under lung protective mechanical ventilation (unpublished preliminary data).’

- **Peer-reviewer’s comment:** ‘...to compare confounding variables such as ... mechanical versus manual pronation...’ - According to comment, the following text has been added: ‘Manual prone positioning proves to be cost-effective since it can be achieved with a sheet or an assistive device (e.g. Vollman Prone Positioning Device). It is a simple technique and allows full access to the patient. The main disadvantage of the method is that it requires additional highly skilled nursing resources. The patient’s size and the number of lines will eventually determine the number of people required for the turn; it can take four or more staff

members to accomplish safely. On the other hand, automated prone-positioning needs one man, minimizes risk during turning and can provide continuous rotation if required according to patient's needs and responses. Unfortunately, the cost of automated prone-positioning beds is very high. Besides, quick access to the patient and abdomen release during mechanical ventilation in prone position are also a concern. To the best of our knowledge, in the literature there are no studies comparing manual and automated prone positioning and the user experience for automated prone positioning remains limited.'

- **Peer-reviewer's comment:** *'Table 1 is a little confused, because all of the data in one line, please separate it and rewrite it according to the original definition'.* - According to comment, the table has been redesigned.

During the revision of the manuscript we have rewritten part of the 'Core tip' and 'Conclusions'. We have also revised the language of the manuscript, we have updated the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review and we have signed the Copyright Assignment form.

Yours Sincerely,

On behalf of all the co-authors



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