Reviewer’s report

Title: Protective ventilation with high versus low positive end-expiratory pressure during one-lung-ventilation for thoracic surgery (PROTHOR): Study protocol for a randomized controlled trial

Version: 0 Date: 19 Dec 2018

Reviewer: Brian O’Gara

Reviewer's report:

The authors should be congratulated for designing and conducting a large-scale multicenter clinical trial that will undoubtedly inform intraoperative anesthesia practice for thousands of patients per year around the world.

The manuscript is well compiled and the methods are clear. I am recommending publication, but would like the authors to consider a few points.

1) Definition of postoperative pulmonary complications

The ESA and ESICM in 2015 created a consensus definition of postoperative pulmonary complications in part to aid in strengthening the quality of perioperative research through the use of standard definitions.


The authors have chosen a similar but ultimately different set of complications to include in their definition of PPCs that is inconsistent with this consensus definition. Although there are many recent trials that have been performed with a non-standard composite outcome (ie pulmonary and non-pulmonary complications IMPROVE, PPV), this can create a few issues.

a) Using a non-standard definition of PPCS could limit the generalizability of the findings of the proposed trial with regards to comparison between other intraoperative mechanical ventilation trials using PPCs as an outcome (ie PROVHILO, iPROVE.).

b) Including additional non-standard complications into their primary outcome will likely increase the event rate within their study. This has the obvious beneficial effects, leading to narrower confidence intervals and potentially enough power to detect a difference between groups. However, the sample size calculation performed using a baseline PPC incidence from LAS VEGAS is inaccurate. LAS VEGAS' definition of PPC is more consistent with
the ESICM definition, but contains fewer variables than the proposed composite PPC outcome in this proposed study. The event rate in the control group in the proposed study, using these additional endpoints, is likely to be higher than 23%. This could lead to inaccuracies in the sample size calculation which would then lead to a potentially excessive amount of patients being enrolled in the study and subjected to potential risk than what is truly needed to accomplish the study goals.

c) The authors have potentially included complications that are not related directly to VILI. Pulmonary embolism and lung hemorrhage come to mind. If there were a significant contribution from these endpoints in the composite outcome, this would limit the potential argument that a protective ventilator strategy was responsible for a difference in the primary outcome.

Due to these issues, I would recommend using the standard definition of PPCs as the primary outcome in this study. It would lead to a more generalizable, biologically plausible result and make the sample size calculation more accurate. The additional outcomes which are currently included in the composite outcome could be treated as secondary endpoints, or used to create a separate composite outcome (such as "expanded PPCs" or the like). Alternatively, the authors could name the composite outcome something other than PPC to avoid confusion with the standard definition.

2) Application of recruitment maneuvers in the low PEEP group

It is understood that RMs will only be used during certain times in the low PEEP group for surgical reasons or in the incidence of hypoxia, here defined as an SPO2 for more than 1 minute. One concern is if these conditions might be quite frequent in this population, especially when OLV is first initiated, and this could lead to frequent RMs being performed in the group with low PEEP. If the RMs (or a subsequent increase in PEEP) are applied frequently in the low PEEP/no RM group, this could result in contamination of interventions between study groups and thus bias the results of the study towards the null. Since this protocolized response to hypoxia is designed to prevent patient harm, it is understandable why it has been designed this way. Alternatives could be to adjust the definition of hypoxia to a more severe setpoint (lower SpO2 or longer period of desaturation), or at a time further from the initiation of OLV, after hypoxic vasoconstriction has occurred. Because this could potentially increase patient risk, this is something merely for the authors to consider given that the potential sacrifices they would be making in terms of achieving a positive study result the way the protocol is currently defined. It is also noted that the first intervention listed for hypoxia in the low PEEP/no RM group is to increase FiO2.
3) Statistical considerations

a) Page 11, line 40 - Please describe how the authors plan on treating missing data for a 90d endpoint, which is prone to a significant amount of loss to follow up

b) Page 19, line 36 - I would encourage the authors to use this publication as the means to publish their detailed statistical plan, in the interest of transparency of methods. Any changes in the statistical analysis plan that occur after this publication, and after one or more interim analyses, would be scrutinized by future reviewers.

4) Minor points

a) Page 6, lines 125 and 133 - please specify the "outcomes" you are referring to

b) Page 7, line 51 - please define persistent hemodynamic instability or intractable shock

c) Page 13, line 34 - please specify the outcome "high dosage of vasoactive drugs" or consider using dosage as a continuously measured variable

d) Page 16, line 35 - Use of a method of lung separation other than a DLT (i.e endobronchial blocker) is listed as an exclusion criteria, and therefore shouldn't be present in your list of collected data for enrolled patients

e) Page 22, line 48 - One could argue that this trial does not focus on the independent effects of PEEP, but rather PEEP and RMs. Consider revising this statement.

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