Author's response to reviews

Title: Protocol for a Systematic Review and Individual Patient Meta-Analysis of Benefit of So-Called Lung-Protective Ventilation-Settings in Patients Under General Anesthesia for Surgery

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Author's response to reviews: see over
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“PROTOCOL FOR A SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS OF BENEFIT OF SO-CALLED LUNG-PROTECTIVE VENTILATION-SETTINGS IN PATIENTS UNDER GENERAL ANESTHESIA FOR SURGERY”

November 06, 2013

Dear editor,

We thank you for giving us the opportunity to submit a revised version of the above-mentioned manuscript.

The comments of the Editors and Reviewers were helpful in improving the manuscript. A point-to-point reply to the reviewer’s comments follows below.

Kind regards, looking forward to your response,

Ary Serpa Neto

Marcus J. Schultz
REVIEWER #1

01. BACKGROUND

As suggested by the reviewer, we included a new sentences explaining the 4 distinct pieces of evidence (RCT and meta-analyses) and also explaining why this IPD analysis is important (in bold).

01.1. I assume that the existing meta-analyses are not IPD, but this is not stated.

“Two conventional meta–analyses of observational studies and randomized controlled trials of intra–operative ventilation…”

01.2. What studies were included in these meta-analyses? Was there an overlap in the studies included in the meta-analyses and were the RCTs mentioned included in any of the meta-analyses?

“However, these two trials were published after the publication of the meta-analyses and were not included in the final analyses.”

01.3. Finally, when were the meta-analyses conducted and is this meta-analysis likely to find new evidence?

“Two conventional meta–analyses of observational studies and randomized controlled trials of intra–operative ventilation published in the beginning of 2013 suggest…”

“This is not an unimportant issue, since use of lower tidal volumes but especially use of higher levels of PEEP could be harmful as well, e.g. by affecting intra–operative hemodynamics [8]. With the use of individual patient data, it will be possible to isolate the real effect of tidal volume from those of PEEP.”
02. METHODS

02.1. Search strategy

Yes. As stated in the first paragraph of the “Methods” (copy below) we will update the previous search done for the other two meta-analyses.

“Published and unpublished observational studies and randomized controlled trials were identified by two previous systematic searches of the literature by our group [6,7]. The list of studies and trials will be updated to identify studies and trial published after the original searches, and thus updated to August 2013.”

02.2. Analysis plan

The length of stay in hospital will be considered as the time from hospital admission to in-hospital death. We included this statement in the “Methods”.

“…4) length of stay in hospital, defined as the time from hospital admission to hospital discharge or death…”

02.3. Completeness of data

As described in the “Methods”, we will collect the data measured hourly in the procedure. For example: in a surgery with eight hours the middle of the surgery is the fourth hour.
02.4. Statistical analysis

02.4.1. Why is tidal volume coded differently for ITT and per protocol?

In the ITT analyses we will include only RCT and patients will be analyzed according to the group of tidal volume that they were included in the original trial (protective or conventional), despite possible violation of the protocol.

In the per protocol analyses we will include RCT and non-RCT and patients will be analyzed according to the tidal volume that they really received.

For example: a patient was randomized to the protective arm but due to violation he received a tidal volume of 11 ml/kg PBW. In the ITT analysis he will be included in the protective arm but in the per protocol analysis he will be included in the group of tidal volume > 10 ml/kg PBW.

02.4.2. Statistical methods need to be defined for all types of outcome, not just time to event. Statistical methods are clear for the restricted cubic splines analysis and cox proportional hazards model but not for binary outcomes.

As suggested by the reviewer, we included a statement about the statistical method for binary outcomes.

“Binary outcomes will be analyzed by the chi-square test and by logistic regression including the same set of covariates as for the Cox proportional-hazards regression model.”

02.4.3. For the generalised linear model used on time-course variables, it states “The model includes two factors: 1) study group (fixed factor)...”. What is meant by study group?
Study groups are the stratification of the patients by the tidal volume size (protective vs. conventional in ITT analyses and ≤ 7 ml/kg PBW vs. 7 – 10 ml/kg PBW vs. > 10 ml/kg PBW in per protocol analyses). We included a statement about it in the protocol.

03. MINOR REVISIONS

03.1. No information is contained in the protocol about dissemination of the results.

As suggested by the reviewer, we included a statement about it in the “Methods”

“The results of this meta-analysis will be sent for publication in a peer-reviewed journal and all collaborators will be included as co-authors of the paper.”

03.2. At the end of the section on “search strategy”, there is information on how authors will be contacted and how data will be extracted from each studies database. This would be more appropriate in the section titled “collection of individual patient data”.

As suggested by the reviewer, we leave it only in the section “Collection of individual patient data”

03.3. The section on “search strategy” suggests that databases will be sent to the corresponding author for data extraction which is inconsistent with the section “collection of individual patient data”. This section states that a datasheet will be sent to authors. More clarity on data collection is needed.

We leave it only in the section “Collection of individual patient data” as “datasheet”.

03.4. My clinical knowledge is limited, so correct me if I’m wrong. Are all surgeries going to be at least, say, 3 hours long? Beginning of surgery measures are in the first hour and end of surgery measures are in the last hour, so I assume one hour is only a small amount of time relative to the duration of the surgery in all cases?
Yes, usually this studies and trials are conducted in patients under at least intermediary risk for postoperative pulmonary complications and the duration of surgery is the main determinant of this risk.

03.5. I would recommend changing the title of this section to “model selection” and adding anything that does relate to model selection into the “statistical analysis” section.

As suggested by the reviewer, we change the title of the section.

03.6. The discussion states “The use of low tidal volume can increase the use of sedatives and muscle relaxants increasing the incidence of ICU delirium and ICU.

The present protocol deals only with patients undergoing general surgery so the use of sedative and muscle relaxants is mandatory for all patients (different from that in mechanical ventilation in the ICU). We included a statement about it.

“In critically ill patients under mechanical ventilation in the ICU, the use of low tidal volume can increase…”

04. DISCRETIONARY REVISIONS

04.1. For the middle of surgery time period, it states “middle of the surgery, beginning of the surgery, defined as the parameters…” Is “beginning of the surgery” a typo – this doesn’t make sense?

We corrected it.
01. The so-called “Lung protective Ventilation” includes low tidal volume AND low Plateau Pressure (< 30 mmHg). This is not stated in the definition and in the inclusion criteria.

We agree with the reviewer however, this is true for patients under mechanical ventilation in the ICU. In the operating room, the majority of studies use only the tidal volume size to define the protective ventilation and this is why we didn’t include the plateau pressure in our definition and inclusion criteria.

02. The AA. should state why an IPD review is appropriate, and which is the expected benefit of an IPD review, compared to a standard one, for the specific research question. Please, consider that if the original data are flawed, even an IPD review will be flawed.

We included a statement about it in the “Background”.

“Neither from the conventional meta–analyses nor from the two randomized controlled trials it is possible to conclude what was really responsible for the improved outcome: the use of lower tidal volumes or the use of higher levels of PEEP or the use of both. This is not an unimportant issue, since use of lower tidal volumes but especially use of higher levels of PEEP could be harmful as well, e.g. by affecting intra–operative hemodynamics [8]. With the use of individual patient data, it will be possible to isolate the real effect of tidal volume from those of PEEP.”

03. The AA will include observational studies, too. How do they assess quality of those studies? Patients in the observational studies are not randomized. Could it bias the IPD review? What if the non-randomized patients group are higher proportion than the randomized one?. The AA should address that point preliminarily.
We agree with the reviewer. To deal with this point we will include the “type of study (RCT vs. non-RCT)” in the multivariate model (stated in the section “Model selection”) and also we will conduct a prespecified subgroup analysis stratifying the patients based on study design (RCT vs. non-RCT, stated in the section “Statistical analysis”).

04. Literature search is limited. IPD review often enables inclusion of studies that could not be included in a standard SR. Thus, unpublished studies should be searched, too (grey literature).

We included it in the section “Search strategy” (…”Published and unpublished observational studies and randomized controlled trials…) and “Collection of individual patient data” (“Corresponding authors will also be contacted about unpublished data to enlarge the clinical data pool”).

05. The validity of the IPD approach requires that data from all the studies (or nearly all) will be available. The AA. should state in which case the analysis will not be performed due to lack of sufficient data from the original trials (Bias due to selective availability of study data).

We included a statement about it in a new section called “Bias”.

“It is expected to obtain at least 90% or more of individuals analyzed in the studies identified in the search strategy to avoid the bias due to selective availability of study data.”

06. The AA. should detail which factors are likely to introduce bias in the review.

We included a new section called “Bias”.
07. Consideration of Outcomes: exploration of interactions between interventions and patient-level characteristics appear to be important. Are the AA going to consider that in outcome of interest?

Yes, as stated in the section “Model selection” and “Statistical plan” patients-level characteristic such as age, gender, ASA, and BMI will be included in the multivariate model. Also, prespecified subgroups analyses based on this groups will be made.