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: 10 Dec 2018

Reviewer: Judith-Irina Pagel

Reviewer's report:

Kiss et al propose a protocol for a currently recruiting, multicenter, randomized IIT investigating a high PEEP with recruitment maneuvers (RM) vs. low PEEP without RM protocol in patients undergoing thoracic surgery with one lung ventilation (OLV).

The study aims to recruit 2378 patients and the primary endpoint and secondary is a collapsed composit for postoperative pulmonary complications (PPC). Postinterventional observation period is 1-5 days concerning endpoints and the 90d mortality to be assessed via phone interview.

Comments:

1.) Overall the PROTHOR protocol aims to tests high PEEP + RM and low PEEP without RM. According to the protocol, a standardized RM shall be executed in the high PEEP group at distinct occasions. The protocol also provides strategies for intraoperative scenarios like hypoxemia. Therein, the authors recommend the standardized RM for the high PEEP group but also for the low PEEP group after initially increasing the FiO2 (page 10, line 9). The authors state in their step by step procedure to increase the PEEP up to 7 cmH2O. But in between the stepwise increase the standardized RM is placed where, according to the procedure, the PEEP can be increased up to a maximum of 20 cmH2O. In Figure 3 the authors show the procedure of the RM and display a PEEP of 10 cmH2O at the beginning (not below or any recommendations for the low PEEP group). This algorithm is proposed for TLV as well as for OLV, but in the OLV setting, CPAP therapy is recommended for both groups up to 20 cmH2O and this is clearly stated for both groups.

It is of course clear that under hypoxia, state-of-the-art rescue strategies must be established to ensure patients' safety. Nevertheless, a clarification is needed to explain if the standardized RM is adapted for the low PEEP group or if statistical analysis will be able to distinguish patients in the low PEEP group with hypoxic rescue using the high peep RM from the rest of the low PEEP group, or if such a patient will be excluded at all from analysis.
2.) Page 13/14 postoperative extrapulmonary complications: Define Sepsis (life-threatening organ dysfunction caused by a dysregulated host response to infection) and sepsis shock (vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia) accordingly. According to the current Sepsis guidelines, the term "severe sepsis" should be avoided.

3.) As far as I know, almitrine is not approved in every European country, this should be stated in the protocol.

4.) Funding: This seems inaccurate. Even if funding is based only on institutional money this should be stated for each participating study center.

5.) Suggestion: page 19, 3rd line: you might want to consider rephrasing "[..]if the trial is going nowhere"

6.) Typos: page 23 line 37/38 space and full stop between "[...]did not achieve the same effect." and "Furthermore...."

Page 24 line 19/20 "[...] but also the incidence of each element separately. f" delete

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