

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial
AUTHORS	ZHOU, zhen-feng; FANG, Jun-biao; WANG, Hong-fa; HE, Ying; YU, Yong-jian; XU, Qiong; GE, Yun-fen; ZHANG, Miao-zun; HU, Shuang-fei

VERSION 1 – REVIEW

REVIEWER	Thijs Rettig Amphia Hospital, the Netherlands
REVIEW RETURNED	05-Apr-2019

GENERAL COMMENTS	<p>The study addresses an interesting and relevant topic, i.e. which PEEP level is best suited in 208 patients undergoing major abdominal laparoscopic surgery. The intervention and primary endpoint are clear.</p> <p>Although I understand that the study is in progress and no changes to the protocol can be made I have some comments, some of which are related to the methodology.</p> <ol style="list-style-type: none">1. the definition for SIRS used in the manuscript is obsolete, while severe sepsis is no longer recognized as a meaningful entity (Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810. doi:10.1001/jama.2016.0287). In addition, the term ALI (acute lung injury) is no longer in use either (ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33). In my opinion, the contemporary definitions should and could be used (i.e. no additional data outside the data collected described in the protocol is required to use the new definitions).2. Some endpoints in the case report form, table 3 (postoperative extra-pulmonary complications within 30 days of surgery), as AKI and DIC, are not mentioned in the manuscript and are not defined.3. the language/grammar is moderate at best (e.g. 'there are increasing studies shown that..')4. 'ropivacaine was administered as local anesthetic..'page 19. What is the route of administration?5. The authors will analyze all secondary endpoints separately (>10), the study has not enough power to perform this analysis.6. different verb tenses are used interchangeably throughout the manuscript (e.g. Abstract: '...standard perioperative fluid..will be applied.. The primary endpoint was...')
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REVIEWER	Ary Serpa Neto Hospital Israelita Albert Einstein São Paulo Brazil
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	<p>The authors present a protocol for a study assessing the impact of PEEP in the incidence of PPC in patients undergoing laparoscopic surgery. The protocol is well written and the authors should be acknowledge. Since, as a reviewer of protocol, our position is not to mandate changes in the original protocol I just have some suggestions to improve this report:</p> <p>METHODS</p> <ol style="list-style-type: none"> 1. I suggest improving the report of the definition of PPC (the primary outcome) 2. I suggest considering multiple imputation for missing vaue instead of imputation by the median 3. I suggest rporting how the secodary outcomes will be handled in the statistical part
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Thijs Rettig

Institution and Country: Amphia Hospital, the Netherlands

Please leave your comments for the authors below

The study addresses an interesting and relevant topic, i.e. which PEEP level is best suited in 208 patients undergoing major abdominal laparoscopic surgery. The intervention and primary endpoint are clear.

Although I understand that the study is in progress and no changes to the protocol can be made I have some comments, some of which are related to the methodology.

1. the definition for SIRS used in the manuscript is obsolete, while severe sepsis is no longer recognized as a meaningful entity (Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810. doi:10.1001/jama.2016.0287). In addition, the term ALI (acute lung injury) is no longer in use either (ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33). In my opinion, the contemporary definitions should and could be used (i.e. no additional data outside the data collected described in the protocol is required to use the new definitions).

Answer: Thank you for your valuable advice and we have redefined the definitions of SIRS and ARDS by the new definitions. (Methods section, line 19 page 10, line 28-30 page 10 and line 1-30 page 11 in the main document-marked copy.).

2. Some endpoints in the case report form, table 3 (postoperative extra-pulmonary complications within 30 days of surgery), as AKI and DIC, are not mentioned in the manuscript and are not defined.

Answer: We are sorry to make you confused. We have deleted the endpoints that are not mentioned in the manuscript and are not defined such as ALI, Acute myocardial infarction, Coma, AKI and DIC. (case report form).

3. the language/grammer is moderate at best (e.g. 'there are increasing studies shown that..')

Answer: Thank you for your advice and we are sorry to make you confused. We have the used future tense to make the tense consistent in the protocol. Our manuscript has also been revised by one of the companies that Elsevier recommends for English translation services. Thank you so much! We all mention in the main document-marked copy.

We have also corrected those grammatical errors and typos as following:

- 1). Page 10, line 5-7: We have changed "Severe hypoxemia is recorded in cases where the patient requires non-invasive or invasive mechanical ventilation." to "Severe hypoxemia is recorded in cases when the patients require non-invasive or invasive mechanical ventilation." (Methods section, line 5-7, page 10).
- 2). Page 10, line 12-15: We have changed "unilateral or bilateral infiltrate with development of ALI (acute lung 7 injury)/ARDS (acute respiratory distress syndrome) on chest X-ray" to "Chest X-ray demonstrating monolateral or bilateral infiltrate." (Methods section, line 12-15, page 10).
- 3). Page 12, line 3: We have changed "Intensive Care of P Zhejiang Provincial People's Hospital." to "Intensive Care of Zhejiang Provincial People's Hospital" (Methods section, line 20 page 12).
- 4). Page 13, line 4-6: We have changed "The attending anesthesiologist will perform anesthesia strictly according to the research protocol, and will be responsible for data" to "The attending anesthesiologist performs anesthesia strictly according to the research protocol and is also responsible for data" (Methods section, line 4-6, page 13)
- 5). Page 15, line 4-5: We have changed "Fentanyl (1-3 µg/kg) and flurbiprofenaxetil 50 mg was required before remifentanil was stop." to "Fentanyl (1-3 µg/kg) and flurbiprofenaxetil 50 mg are required before remifentanil is stopped." (Methods section, line 4-5 page 15).
- 6). Page 17, line 2-5: We have changed "Analysis will be by intention-to-treat comparing the composite outcome measure at 7 days in the two groups" to "Intention-to-treat (ITT) analyses are performed to compare the composite outcome measure at 7 days in the two groups" (Statistics section, line 2-5 page 17).
- 7). Page 17, line 26-28: We have changed "DMSC will recommend that the study must to be stopped if it is found that the continued conduct of the study compromises patient safety" to "DMSC will recommend that the study must be stopped unless there is evidence that patient will safety". (Methods section, line 26-28 page 17).

4. 'ropivacaine was administred as local anesthetic..'page 19. What is the route of administration?

Answer: We are sorry to make you confused. Ropivacaine is administrated as local anesthetic incision infiltration anesthesia before and at the end of operation respectively. (Methods section, line 3-4 page 15 in the main document-marked copy.).

5. The authors will analyze all secondary endpoints seperately (>10), the study has not enough power to perform this analysis.

Answer: Thank you for your advice and we do agree with you. Sample size is calculated for the primary outcome. However, we have also measure those secondary endpoints and so we will analyze all secondary endpoints separately. This study may have not enough power to make a conclusion for those secondary endpoints separately. However, the information may be useful for calculating the future study,s sample size when those secondary endpoints are the primary outcomes in the future study.

6. different verb tenses are used interchangeably throughout the manuscript (e.g. Abstract: '...standard perioperative fluid..will be applied.. The primary enpoint was...)

Answer: Thank you for your advice and we are sorry to make you confused. We have the used future tense to make the tense consistent in the protocol. We have also corrected those grammatical errors and typos. Our manuscript has also been revised by one of the companies that Elsevier recommends for English translation services. Thank you so much!

Reviewer: 2

Reviewer Name: Ary Serpa Neto

Institution and Country: Hospital Israelita Albert Einstein, São Paulo, Brazil

Please leave your comments for the authors below

The authors present a protocol for a study assessing the impact of PEEP in the incidence of PPC in patients undergoing laparoscopic surgery. The protocol is well written and the authors should be acknowledge. Since, as a reviewer of protocol, our position is not to mandate changes in the original protocol I just have some suggestions to improve this report:

METHODS

1. I suggest improving the report of the definition of PPC (the primary outcome)

Answer: Thank you for your advice and we are sorry to make you confused. We have changed to "The primary endpoint was of PPCs is defined according to a previous report including any new atelectasis or infiltrates on a chest X-ray, respiratory failure (defined as the need for noninvasive or invasive ventilation) or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO₂/FiO₂) < 300 within 7 days after surgery." (Methods, line 14-18, page 9 in the main document-marked copy).

2. I suggest considering multiple imputation for missing value instead of imputation by the median

Answer: Thank you for your valuable advice. Missing values will be replaced by the mean of all plausible data (both groups) of the respective endpoint as reference to a previous literature [1] ([1

Luketina RR, Knauer M, Köhler G, et al. Comparison of a standard CO₂ pressure pneumoperitoneum insufflator versus AirSeal: study protocol of a randomized controlled trial. *Trials*. 2014. 15: 239.). (Methods section, line 21-23 page 16 in the main document-marked copy.).

3. I suggest reporting how the secondary outcomes will be handled in the statistical part

Answer: Thank you for your advice. The primary outcome and secondary outcomes will be all handled by Student's t-test, Mann-Whitney U-test or chi-square test. (Statistics, line 2-3, page 17 in the main document-marked copy).

VERSION 2 – REVIEW

REVIEWER	thijs rettig amphia hospital, breda, the netherlands
REVIEW RETURNED	21-Jun-2019

GENERAL COMMENTS	<p>The topic of this paper is interesting, clinically relevant and worth publishing as I have stated before. However, just as the previous version of this manuscript, the grammar and the sentence's structure is often sloppy. This has to be resolved. When reading the paper this is quite obvious, some examples are:</p> <ul style="list-style-type: none">- postoperative pulmonary complications is abbreviated as PPC and PCC interchangeably- 'DMSC will recommend that the study must to be stopped unless there is evidence that patient will safety'. This an unfinished sentence on page 17- the study endpoints paragraph states "The Berlin Definition of ARDS(cute Respiratory Distress Syndrome)". I suppose the authors define ARDS according to the Berlin criteria.
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	- one of the objectives is to examine the effect of different PEEP levels on hypotension, but hypotension is not defined in the paper.
REVIEWER	Ary Serpa Neto Hospital Israelita Albert Einstein Brazil
REVIEW RETURNED	17-Jun-2019
GENERAL COMMENTS	All my questions were addressed. However, I strongly suggest to the authors to prepare a full statistical analysis plan before the closing of the database. If necessary, they should look for a statistician or researcher experienced in RCTs

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Ary Serpa Neto

Institution and Country: Hospital Israelita Albert Einstein

Brazil

1. All my questions were addressed. However, I strongly suggest to the authors to prepare a full statistical analysis plan before the closing of the database. If necessary, they should look for a statistician or researcher experienced in RCTs

Answer: Thank you for your advice. Statistical analysis was planned according to a statistician experienced in RCTs named Yun-xian YU (Department of Epidemiology and Health Statistics, School of Public Health, Zhejiang University).

Reviewer: 1

Reviewer Name: thijs rettig

Institution and Country: amphia hospital, breda, the netherlands

The topic of this paper is interesting, clinically relevant and worth publishing as I have stated before. However, just as the previous version of this manuscript, the grammar and the sentence's structure is often sloppy. This has to be resolved. When reading the paper this is quite obvious, some examples are:

1. postoperative pulmonary complications is abbreviated as PPC and PCC interchangeably

Answer: Thank you for your advice and we are sorry to make you confused. We have confirmed that the postoperative pulmonary complications is abbreviated as PPCs. (Abstract section, line 8, page 4; Background section, line 12,26,27, and 29, page 7 in marked copy).

2. 'DMSC will recommend that the study must to be stopped unless there is evidence that patient will safety'. This an unfinished sentence.

Answer: We are sorry to make you confused. We have finished the sentence as "DMSC will recommend that the study should be stopped unless there is evidence that patient is safety (a

between-group difference in serious adverse events or in 30- day mortality is found).” (Methods section, line 20-23, page 17 in marked copy).

3. the study endpoints paragraph states "The Berlin Definition of ARDS(cute Respiratory Distress Syndrome)'. I suppose the authors define ARDS according to the Berlin criteria.

Answer: Yes, we define ARDS according to the Berlin criteria. Thank you for your advice. We revised as “ARDS (Acute Respiratory Distress Syndrome) is defined according to the Berlin criteria.” (Methods section, line 12-13, page 10 in marked copy).

4. one of the objectives is to examine the effect of different PEEP levels on hypotension, but hypotension is not defined in the paper.

Answer: Thank you for your advice and we are sorry to make you confused. Hypotension is not one of the objectives. So we delete the hypotension. (Methods section, line 11, page 8 in marked copy).

VERSION 3 – REVIEW

REVIEWER	Thijs Rettig Amphia Hospital, The Netherlands
REVIEW RETURNED	22-Aug-2019
GENERAL COMMENTS	The manuscript has been clearly improved. I have no further comments.