OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

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You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Iranian Journal of Pediatrics
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Peer Review Report for "The Stepwise Slow Titration of Positive End-Expiratory Pressure Before the End of General Anaesthesia Improves Lung Mechanics in Children: A Randomized Open Label Clinical Trial"

Author(s): Ana Dragoljub Mandras, Maja Sujica, Nikola Stankovic, Sladjana Vasiljevic, Vesna Milojkovic, Dusica Simic

Review Timeline:

Submit Date:	15 Feb 2020
Revised Date:	6 May 2020
Accepted Date:	7 Jun 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Bulent Karadag: Reviewer | **Revision** (0) — 17 Mar 2020

Dear AE,
Thanks to the authors for submitting this interesting paper investigating lung dynamics. The method is appropriate. Results are presented clearly. Referencing and citations are correct. English is fluent and easy to understand. My decision is to accept it for publication.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 18 Mar 2020

Dear AE
It is a great pleasure to be invited as a reviewer of this manuscript. Following are my comments.
- Title should be revised, 20 minutes is not proper to be inserted in the title.
- The running title should be summarized as well.
- There are some defects in grammar and writing style, which require to be corrected.

- In the text, the complete form of some abbreviations such as ETCo2 and PEEP have been noted after the first time that they had been abbreviated.
- It has been mentioned that all types of surgeries, except cardiothoracic, were enrolled in the survey, it is actually a wide range, inclusion criteria should be revised more specifically.
- Furthermore, exclusion criteria could be presented better
- Please insert the keywords at the end of the abstract.
- How did you find the proper sample size? Based on which formula.
- Why did you perform invasive BP monitoring for all your pediatric patients? Based on your inclusion criteria and the type of surgeries and considering the potential harm was it really indicated for all cases?
- Please explain more about the characteristic of your hospital, private, referral, governmental
- In the method section please explain the exact meaning of gas exchange monitoring.
- Please explain the method of blinding and randomization.
- Result section should be presented numerically with more details, all results have been pointed to the tables.
- In table 2 a separate P-value should be presented for T1, T2, and…
- The phrase significant should be added before the differences.
- Discussion section is a challenging part in which the results of similar studies and the reason for the differences should be discussed. In this paper, it has not been considered.
- Please update the references, the manuscript should be revised according to new ones. Obviously, several 2019-2020 researches have been published.

Warm Regards

REFEREE: Associate Editor | **Revision** (0) 18 Mar 2020

Dear EIC,

The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.

Kind regards,

REFEREE: EIC | **Revision** (0) 18 Mar 2020

Dear Author,

Thank you for submitting your manuscript to Iran J Pediatr. Your manuscript has now been reviewed by two reviewers and an Associate Editor. I now have the reports of the Referees, which suggest that your manuscript might be suitable for publication following a number of revisions. I attach some reviewer comments and invite you to submit a revised version of your manuscript addressing the points made.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Abstract 101801 – answer to reviewers

“Reviewer 1:
Thank you for submitting this interseting paper investigating the lung dynamics. Method is appropriate. Results are presented clearly. Referencing and citations are correct. English is gluent and easty to understand. My decision is to accept for publication.”

Answer to reviewer 1

Thank you very much for your review.

Reviewer 2:

-Title should be revised, 20 minutes is not proper to be inserted in title.
-Running title should be summarized as well.
-There are some defects in grammar and writing style, which require to be corrected.
-In the text, the complete form of some abbreviations such as ETCo2 and PEEP have been noted after the first time that they had been abrivated.
-It has been mentioned that, all types of surgeries, except of cardiothoracic were enrolled the survey,it is actually a wide range, inclusion criteria should be revised more specifically.
-Furthermore exclusion criteria could be presented better- please insert the key words at the end of abstract.
-How did you find the proper sample size? Based on which formula.
-Why did you perform invasive BP monitoring for all your pediatric patients? Based on you inclusion criteria and the type of surgeries and considering the potential harm was it really indicated for all caeses?
-Please explain more about the characteristic of your hospital, private, referral, governmental
-In method section please explain the exact meaning of gas exchange monitoring.
-Please explain about the method of blinding and randomization.
-Result section should be presented numerically with more details, all results have been pointed to the tables.
-In table 2 a seprate Pvalue should be presented for T1,T2 and…
-The phrase significant should be added before the differences.

- Discussion section is a challenging part in which the results of similar studies and the reason of the differences should be discussed.In this paper it has not been considered.
-Please update the refrencess,the manuscript should be revised according to new ones.Obviousely several 2019-2020 resarches have been published.

Answer to reviewer 2

Thank you very much for your review. The following changes according to suggestion were made as well as answers to your question. Some of them are adjusted to fit the paper, bold yellow. I'm happy to answer if anything else is needed.

-Title should be revised, 20 minutes is not proper to be inserted in title.
-Running title should be summarized as well.

Stepwise Slow Titration of Positive End-Expiratory Pressure Before The End of General Anaesthesia Improves Lung Mechanics in Children: A Randomized Open Label Clinical Trial

Running head:
Intraoperative PEEP titration improves lung mechanics in preschool children

-There are some defects in grammar and writing style, which require to be corrected.

Re-checking was performed again by native English speaker

-In the text, the complete form of some abbreviations such as ETCo2 and PEEP have been noted after the first time that they had been abrivated.

"adjusted to keep end-tidal CO_2 ($EtCO_2$) 35-45 mmHg, PEEP 3 cmH_2O"

"lack of PEEP and muscle paralysis potentiate"

-It has been mentioned that, all types of surgeries, except of cardiothoracic were enrolled the survey,it is actually a wide range, inclusion criteria should be revised more specifically.
-Furthermore exclusion criteria could be presented better- please insert the key words at the end of abstract.

"Inclusion criteria were: age 3-7 years, ASA I and II, children undergoing orthopaedic, reconstructive, abdominal or urology surgery. Exclusion criteria were: present cardiac comorbidity, respiratory comorbidity, current or recent (up to 4 weeks) upper airway infection, children scheduled for cardiothoracic surgery and contraindication to anaesthetics used in study protocol."

"Key words: barotrauma, positive end-expiratory pressure, paediatric patients"

-How did you find the proper sample size? Based on which formula.

The paper presented to you for revision is a part of PhD thesis designed to investigated safety and efficacy of intraoperative PEEP titration on lung function in preschool children during general anesthesia (editor is informed in Cover letter). In present paper we discuss lung mechanics. In paper published by IJP in November 2019, **you can see it as reference 11**, we discussed different parameters. One of them is FiO_2/PaO_2 index, outcome that we used to form our sample size in PhD thesis itself.

Since this is a substudy, as stated in Introduction section, sample used here is the same in previously published paper.[11] In brief, calculation of the sample size was based on expected effect of PEEP on PaO_2/FiO_2 with $\alpha = 0.05$ and study power of 80%. This parameter we discussed in previously published paper.[11] The number needed was read from statistical tables and it was 30 participants per group.[16] A further 5 were added in each group to compensate for dropouts.We needed 35 participants per group.

-Why did you perform invasive BP monitoring for all your pediatric patients? Based on you inclusion criteria and the type of surgeries and considering the potential harm was it really indicated for all caeses?

As you know, manipulating with positive pressure ventilation pressures doesn't affect only lung but also filling pressures of cardiac chambers. One of the criteria for aborting the PEEP titration was hypotension. Our PEEP titration is designed to be uninterrupted and as such requires continuous monitoring of blood pressure to understand the behavior of blood pressure on presented PEEP levels and to serve to spot hypotension immediately. Again I'm going to have to refer to Introduction section and reference 11.

-Please explain more about the characteristic of your hospital, private, referral, governmental

My hospital is tertiary pediatric national, teaching institute (hospital). We treat premature babies, neonates and children up to 16 years of age. We have 5000 general anesthesia per year, me personally 800 per year (premature babies, neonates, preschool and school children and adolescents) (I have 13 years of experience, 7 years as specialist of anesthesiology and intensive care therapy). We cover everything but neurosurgical patients. We also treart patients in ICU -

neonatal, pediatric and cardiac. If you would be interested to visit I'll glad to host you. You can contact me by e mail.

-In method section please explain the exact meaning of gas exchange monitoring.

Blood gas analysis - partial pressures of CO_2 and O_2

-Please explain about the method of blinding and randomization.

After triage recruits were randomly assigned in a 1:1 ratio, using "sealed envelope" technique into two groups; interventional (n=35) and control (n=35). The box containing 70 envelopes with allocation instruction (paper with group; I –interventional group; C – control group) was used to allocate patients randomly. Anesthetist in charge pulled the envelope from the box and allocate patient to experimental or control group.

In Disussion section:….The limitation of our study is open label design…

-Result section should be presented numerically with more details, all results have been pointed to the tables.

Independent T test for delta between groups revealed that there was a statistically significant difference in the magnitude of change in investigated parameters between the groups and all were P<0,001: Cdyn (Δ TI-TII I group -3.2vs C group 0.63); PPI(Δ TI-TII I group -0.57 vs C group 0.11) and Paw (Δ TI-TII I group -0.63 vs C group 0.0)

-In table 2 a seprate Pvalue should be presented for T1,T2 and…

Table 2 Outcome variables between interventional and control group

	interventional	**control**	**p[a]**
Cdyn			
T I	30.1 (27.4-32.8)	27.8 (24.9-30.6)	0.225
T II	33.4 (30.1-36.7)	27.1 (24.3-30.0)	0.005
Δ TI-TII	-3.2 (-4.5- -1.9)	0.63 (0.25-1.01)	<0.001
PIP			
T I	10.9 (10.5-11.3)	10.6 (9.9-11.4)	0.530

T II	11.5 (11.2-11.8)	10.5 (9.8-11.3)	0.020
Δ TI-TII	-0.57 (-0.9- -0.3)	0.11 (0.0-0.2)	<0.001
Paw			
T I	7.14 (6.8-7.5)	6.1 (5.8-6.5)	<0.001
T II	7.8 (7.6-7.9)	6.1 (5.8-6.5)	<0.001
Δ TI-TII	-0.63 (-0.9 – -0.3)	0.0 (0.0-0.0)	<0.001

Results are presented as mean (95% CI); T I -20 minutes before the end of surgery; T II -before extubation; [a] Independent samples t test

-The phrase significant should be added before the differences.

It has been added

- Discussion section is a challenging part in which the results of similar studies and the reason of the differences should be discussed. In this paper it has not been considered.

Discussion and referencing were corrected according to subject and suggestions.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 23 Apr 2020

Dear AE,
- As this article is a clinical trial it must have the IRCT code. Please note it in ethical considerations. Trial registration: NCT03745443 indicated in this research has been expressed by another published article, “Slow Positive End-Expiratory Pressure Titration During General Anesthesia with Muscle Paralysis Improves Lung Function Without Compromising Hemodynamic Stability in Preschool Children: A Randomized Control Clinical Trial”
To my knowledge, each clinical trial has a unique code. Please explain about it.
- There are still some grammatical and writing defects in the text. For example “Due to the goals of our clinical trial mentioned in the Introduction and well know the effect of PEEP on filling pressures we monitored invasive blood pressure (IBP) and EKG.” Needs to be revised as below:
Due to…., in the introduction section….well known…..effects… electrocardiogram (ECG or EKG)
And many other parts have the same problem.
- Please explain about the hospital in which this research has been conducted?
- The type of surgeries indicated in inclusion criteria has not been considered in the Material & methods part of the abstract section;
- A flow diagram should be inserted. How many children and why were excluded during the survey.
REGARDS

REFEREE: Associate Editor | **Revision** (1) 24 Apr 2020

Dear EIC,
The revised version has been reviewed. The revised version seems better than the original manuscript. But I think authors should try to improve their manuscript based on other reviewers' comments.
Thanks.

REFEREE: EIC | **Revision** (1) 24 Apr 2020

Dear Author,
The second round of peer review of your manuscript is completed. I now have the reports of

the Referees, which suggest that your manuscript needs more correction.

Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Answer to Reviewer

Dear reviewer,

Thank you for taking the time to review my paper. Below you will find my answers to your suggestions.

-As this article is a clinical trial it must have the IRCT code. Please note it in ethics considerations. Trial registration: NCT03745443 indicated in this research has been expressed by an other published article , "Slow Positive End-Expiratory Pressure Titration During General Anesthesia with Muscle Paralysis Improves Lung Function Without Compromising Hemodynamic Stability in Preschool Children: A Randomized Control Clinical Trial"
To my knowledge each clinical trial has a unique code. Please explain about it.

Your suggestion regarding the identification number is highly appropriate. I would like to clarify the following in order to avoid any possible confusion. The clinical trial registered under registration number NCT03745443 has multiple outcome variables. To my knowledge, more than one paper can be written from the data obtained in one trial, which I did; first paper was published in November in IJP and another is the one you are currently reviewing. I used the same registration number because I think it is important for readers to know the origin of the data, methodology, etc. I have not come across any information that would suggest otherwise, but of course, I may not be right. Please take this explanation into consideration. If you still think that I should re-register the research, I would gladly do it so that I can publish my paper in your journal.

-There are still some grammatical and writing defects in the text. For example "Due the goals of our clinical trial mentioned in Introduction and well know effect of PEEP on filling pressures we monitored invasive blood pressure (IBP) and EKG." Needs to be revised as below:
Due to….,in the introduction section….well known…..effects… electrocardiogram (ECG or EKG)
And many other parts have the same problem.

The paper was revised by linguist and I think that now it is ok. Please suggest if otherwise.

Please explain about the hospital in which this research has been conducted?

My hospital is tertiary pediatric national, teaching institute (hospital). We treat premature babies, neonates and children up to 16 years of age. We have 5000 general anesthesia per year, me personally 800 per year (premature babies, neonates, preschool and school children and adolescents) (I have 13 years of experience, 7 years as specialist of anesthesiology and intensive care therapy). We cover everything but neurosurgical patients. We also treat patients in ICU -

neonatal, pediatric and cardiac. If you would be interested to visit and exchange experience when COVID19 pandemic stops, I'll be more than happy glad to be your host. You can contact me by e mail : ana_mandras@yahoo.com

The type of surgeries indicated in inclusion criteria has not been considered in the Material & methods part of abstract section;

I've inserted it in the text as follows:

"Methods: This was an open label, single tertiary centre randomized controlled clinical trial**.** The study population included 70 preschool children, ASA I and II, scheduled for orthopaedic, reconstructive, abdominal or urological surgery."

A flow diagram should be inserted. How many children and why were excluded during the survey.

I've submitted CONSORT flow chart as separate document (pdf.) as indicated on the platform but, now I put it at the end of text for you to see. I've inserted the comment in text, it goes as follows>

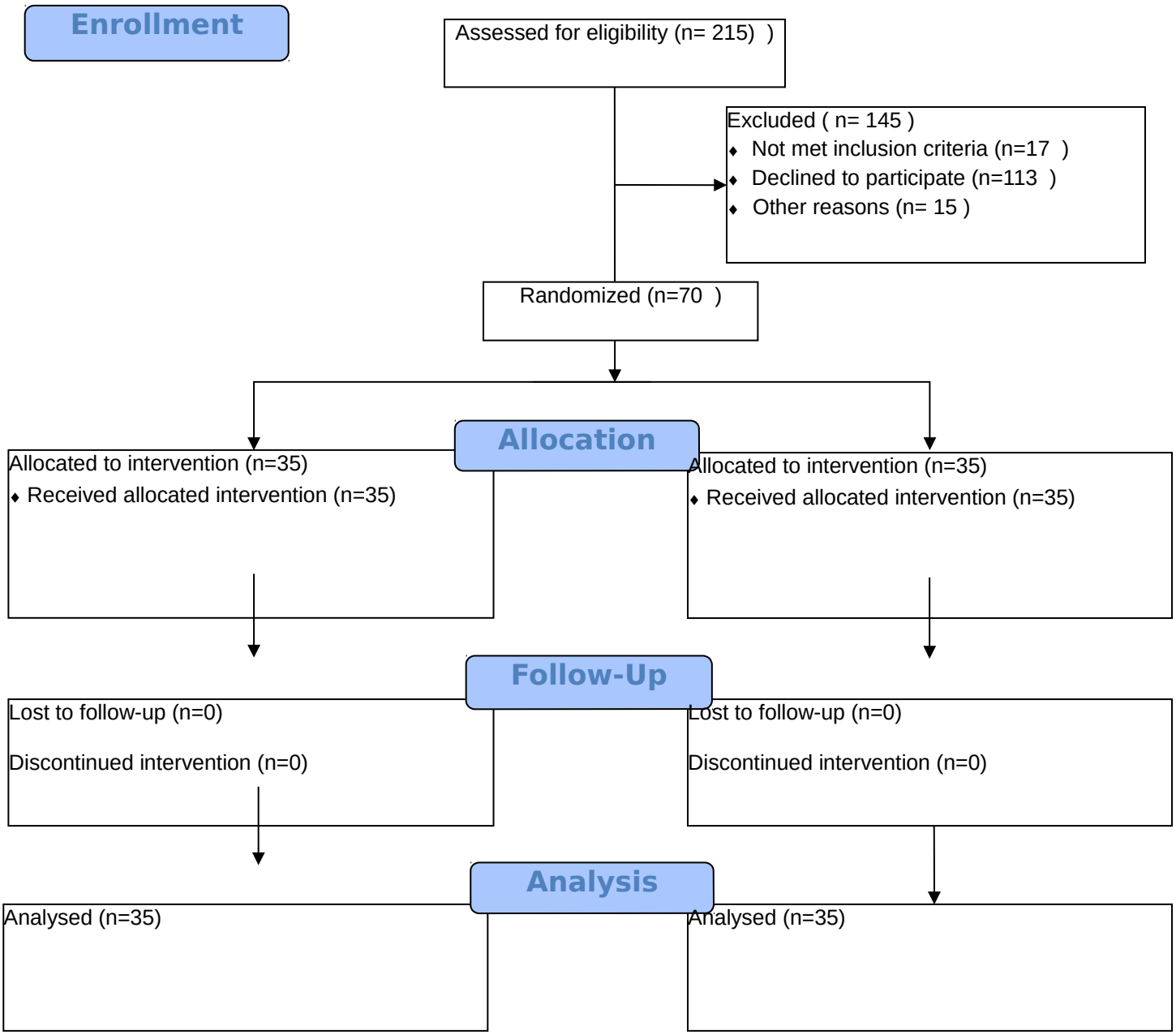
"Of 486 children scheduled for surgery between January 2017.-June 2017, 271 were younger than 3 or older than 7 years of age, 113 refused participation, 10 had upper respiratory tract infections, 7 had a chronic heart or lung condition and 15 didn't show up for surgery. Recruited participants (n=70) finished the study and were analysed, there were no dropouts."

Please inform me if anything else needs to be corrected.

Regards

Dr Ana Mandras

CONSORT 2010 Flow Diagram



OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (2) 30 May 2020

Dear AE,
Thanks for your kind invitation, I peered the revised manuscript. In my idea, the respected authors have considered the comments.
REGARDS

REFEREE: Associate Editor | **Revision** (2) 5 Jun 2020

Dear EIC,
The authors have modified the manuscript accordingly and have provided specific answers in an accurate manner. I suggest that this version is suitable for publication in the Iran J Pediatr.
Thanks.

REFEREE: EIC | **Revision** (2) 7 Jun 2020

Dear Author,
The second round of peer review of your manuscript has been completed, and I am pleased to inform you that your manuscript has now been accepted for publication in our journal.
Thanks.