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.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brieflands.com/briefland/knowledgebase/category/tree.html#opr.html

Iranian Journal of Pediatrics
Article DOI: 10.5812/ijp.102118
Published in: Iranian Journal of Pediatrics: 30(4); e102118

Peer Review Report for "Effects of High-Dose Selenium Supplementation on Oxidative Stress and Inflammatory Markers in Critically Ill Children After Gastrointestinal Surgery: A Randomized Clinical Trial"

Author(s): Fatemeh Roudi, Gholamreza Khademi, Golnaz Ranjbar, Houshang Rafatpanah, Habibollah Esmaily , Mohsen Nematy

Review Timeline:

Submit Date:	24 Feb 2020
Revised Date:	7 Apr 2020
Accepted Date:	14 Apr 2020

Revision (0)

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

REFEREE: Reviewer | **Revision** (0) 10 Mar 2020

Dear AE,
Comments for the authors:
1. Other trace elements such as zinc, copper, chromium, and manganese are antioxidants, which did not explain their role.
2. Please explain the Inclusion and exclusion criteria.
3. For the determination of plasma selenium levels, what is the method used?
4. On what basis is the dose of selenium calculated? (References?)
5. Selenium deficiency has not been shown in which group of patients. (Malnutrition?)
6. Please Update references.
Thanks.

REFEREE: Reviewer | **Revision** (0) 19 Mar 2020

Dear AE,
The authors investigated the effects of high-dose selenium supplementation on oxidative stress and inflammatory markers in critically ill children after gastrointestinal surgery, which is a novel and important subject. The paper is generally very good. The introduction provided sufficient background and logic behind the study. The study design and methods are well detailed. The results are provided in organized way. The discussion properly explained the results of this study as well as comparison with other studies. The references are adequate and recent. The paper is well-written with good language and structure.
Thanks.

REFEREE: Reviewer | **Revision** (0) 21 Mar 2020

Dear AE,
Thank you for the opportunity to review the manuscript entitled “Effects of High-dose Selenium Supplementation on Oxidative Stress and Inflammatory Markers in Critically Ill Children after Gastrointestinal Surgery: A Randomized Clinical Trial” submitted to the Iranian Journal of Pediatrics. The authors have designed a randomized clinical trial to study to assess the effects of high-dose selenium supplementation on the improvement of inflammatory and oxidative stress indices, as well as clinical outcomes, in pediatric patients with severe oxidative stress and inflammation following major gastrointestinal surgeries. Overall, the manuscript is well-written and I could not identify any major flaws in the methodology of this paper. However, the paper requires a moderate revision and several comments have to be addressed by the authors.
1. Plagiarism detection in the manuscript.
I have screened the manuscript for plagiarism with iThenticate and the paper is original.
2. The analysis method of the manuscript
The paper should adhere to the CONSORT 2010 checklist for randomized controlled trials. Please check whether all aspects provided in the CONSORT 2010 checklist have been addressed and upload the completed checklist with the revised version of your paper.
3. Results
The results are interesting, but I feel that the Results section should be rewritten. It is superfluous and it is difficult to follow the text. Please try to be more concise and to state the main ideas, use abbreviations when appropriate etc.
I have some comments regarding the Results and Discussions:
• Apart from being a component of the enzyme glutathione peroxidase, selenium is also a component of the iodothyronine deiodinases. Do you believe that your results can be re-interpreted in this context as well? Did the thyroid via thyroid hormones play a role in the evolution of the critically ill children?
• Why didn’t you assess classical markers of inflammation as well? Fibrinogen, erythrocyte sedimentation rate, ferritin, neutrophil-to-lymphocyte ratio etc? These markers have been shown to correlate with oxidative stress levels in other conditions. Also, the authors should explain in more detail the role of oxidative stress in inflammation in the disorders presented in the paper. Please see:
https://doi.org/10.37358/RC.20.1.7837
https://doi.org/10.37358/RC.19.10.7581

https://doi.org/10.37358/RC.19.6.7314

• It is not completely clear to me whether the subjects received other vitamins/minerals as well. Vitamin C and vitamin E are potent antioxidants that also reduce the levels of oxidative stress and contribute to the prevention of infections. Please check:
https://www.hindawi.com/journals/omcl/2014/158135
https://doi.org/10.37358/RC.19.2.6977

• I think the manuscript would benefit from a graphical abstract or a colourful figure describing the possible mechanisms of action of selenium as concluded from this randomized clinical trial.

4. Correct referencing and citations

The references are cited correctly and this section is arranged in accordance with the journal's guidelines.

5. Correct and proper English writing

The level of English is adequate. Maybe a spellcheck using the free version of Grammarly would be useful.

6. Your decision about this manuscript (accept/revision/reject).

At this point, the manuscript requires a (moderate) revision.

Thanks.

REFEREE: Associate Editor | **Revision** (0) 22 Mar 2020

Dear EIC

The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.

Kind regards,

REFEREE: EIC | **Revision** (0) 22 Mar 2020

Dear Authors,

Thank you for submitting your manuscript to Iran J Pediatr. Your manuscript has now been reviewed by three 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.

Dear reviewers and editors;

We appreciate your valuable comments, amendments are done according to your request in below and the main manuscript file:

Reviewer 1:

1. Other trace elements such as zinc, copper, chromium, and manganese are antioxidants, which did not explain their role.

All the patients were visited and monitored daily by clinical nutritionists. Moreover, not receiving concomitant supplementations (e.g., vitamin C, vitamin E, beta-carotene, zinc, copper, chromium, and manganese) were also monitored by the clinical nutritionists.

2. Please explain the Inclusion and exclusion criteria.

As it is mentioned in the manuscript:

“The patients were aged 0-10 years and underwent major GI surgeries, including esophageal atresia, intestinal atresia, biliary atresia, intestinal obstruction, omphalocele, Hirschsprung's disease, and gastric pull-up. The patients were admitted to the ICU after major GI surgeries due to their medical indications and were therefore considered eligible for recruitment. The exclusion criteria of the study were as follows: 1) not receiving nutritional support care within the first 24-48 hours postoperatively; 2) earlier PICU discharge than five days after the surgery; 3) sensitivity to sodium selenite or its contents; 4) baseline (preoperative) serum selenium concentrations of >106 µg/l; 5) diagnosis of autoimmune disorders, cancer, severe hepatic failure, renal failure, HIV infection, and severe sepsis upon admission; 6) history of chemotherapy and radiotherapy within the past month; 7) laboratory/clinical symptoms of selenium intoxication; 8) severe and active bleeding and 9) preterm neonates.”

3. For the determination of plasma selenium levels, what is the method used?

In the “Laboratory Assays” section of the manuscript, we have mentioned that “Serum and urine selenium were analyzed using an atomic absorption spectrometer (Perkins-Elmer HGA-700 Graphite Furnace, USA).”

4. On what basis is the dose of selenium calculated? (References?)

Our research team established several expert panels on the dose determination in the study, and there were numerous concerns in this regard. After several discussion panels on the current literature, it was concluded that this dose (20 µg/kg/d) will be safe and probably beneficial for short-term supplementation in the patients admitted in the pediatric intensive care unit (PICU). Some evidence in this regard has been presented, as follows:

“The research team established several expert panels on the dose determination at the beginning of the study, and there were numerous concerns in this regard. The optimal dose for short-term selenium supplementation in the children was estimated using the NAIR equation (equivalent dose for children: 48 µg/kg/d) (1-3).
Considering the estimated selenium dose of 48 µg/kg/d based on the NAIR formula in terms of the established recommended dietary allowance (RDA) of selenium (2 µg/kg/d) (4), studies are lacking on high-dose selenium supplementation (>10 µg/kg/d) in children (5). In this regard, the selenium dose has been determined to be within the range of 10-48 µg/kg/d, and therefore 20 µg/kg/d of selenium is recommended for children admitted to the ICU after gastrointestinal surgeries. “

5. Selenium deficiency has not been shown in which group of patients. (Malnutrition?)

The main rationale of our study was that the daily requirement of selenium may increase in the acute phase following major surgeries due to short-term metabolic and antioxidant maintenance needs. Consequently, the patients may benefit from high-dose selenium administration. Therefore, our focus was on an increased requirements of selenium rather than correcting the deficient levels.

However, as it is mentioned in the “results” section, Table 1, and the “Discussion” section; only 21% of our patients (n=14) had an optimal selenium concentration at the beginning of the study and there was no significant difference between the two studied groups. According to the results

of the present study and previous studies in Iran, selenium deficiency prior to major surgeries cannot be overlooked in various populations (6, 7).

6. Please Update references.

Amendments are done according to your request, we have checked and corrected the “References” section by Endnote software.

Reviewer 2:

Thank you for the opportunity to review the manuscript entitled “Effects of High-dose Selenium Supplementation on Oxidative Stress and Inflammatory Markers in Critically Ill Children after Gastrointestinal Surgery: A Randomized Clinical Trial” submitted to the Iranian Journal of Pediatrics. The authors have designed a randomized clinical trial to study to assess the effects of high-dose selenium supplementation on the improvement of inflammatory and oxidative stress indices, as well as clinical outcomes, in pediatric patients with severe oxidative stress and inflammation following major gastrointestinal surgeries.

Overall, the manuscript is well-written and I could not identify any major flaws in the methodology of this paper. However, the paper requires a moderate revision and several comments have to be addressed by the authors.

Many thanks for your consideration, it would be our honor to hear these statements.

1. Plagiarism detection in the manuscript.

I have screened the manuscript for plagiarism with iThenticate and the paper is original.

Many thanks for your consideration.

2. The analysis method of the manuscript

The paper should adhere to the CONSORT 2010 checklist for randomized controlled trials. Please check whether all aspects provided in the CONSORT 2010 checklist have been addressed and upload the completed checklist with the revised version of your paper.

Amendments are done according to your request and we have completed the CONSORT 2010 checklist for the manuscript. Please visit the checklist as a supplementary file.

3. Results

The results are interesting, but I feel that the Results section should be rewritten. It is superfluous and it is difficult to follow the text. Please try to be more concise and to state the main ideas, use abbreviations when appropriate etc.

Amendments are done according to the reviewers' request, the "results" section is simplified and the main content is concise.

I have some comments regarding the Results and Discussions:

• *Apart from being a component of the enzyme glutathione peroxidase, selenium is also a component of the iodothyronine deiodinases. Do you believe that your results can be re-interpreted in this context as well? Did the thyroid via thyroid hormones play a role in the evolution of the critically ill children?*

Yes indeed, we added the following statement to the "discussion" section as you requested:

"Although the levels of triodothyronine (T3) is low and reverse T3 is elevated, and also TSH and thyroxin (T4) are low, parallel with the low plasma selenium levels and severity of the disease in critical illnesses, it is reported that selenium supplementation play an indirect role thorough the reduction of cytokine release in increasing the expression levels of thyroid hormones (8). Therefore, thyroid hormones may play a role in the evolution of the studied critically ill children; however, further studies are required to investigate the exact relation between selenium and thyroid selenoenzyme expression levels via critical illnesses.

• *Why didn't you assess classical markers of inflammation as well? Fibrinogen, erythrocyte sedimentation rate, ferritin, neutrophil-to-lymphocyte ratio etc? These markers have been shown to correlate with oxidative stress levels in other conditions. Also, the authors should explain in more detail the role of oxidative stress in inflammation in the disorders presented in the paper. Please see:*

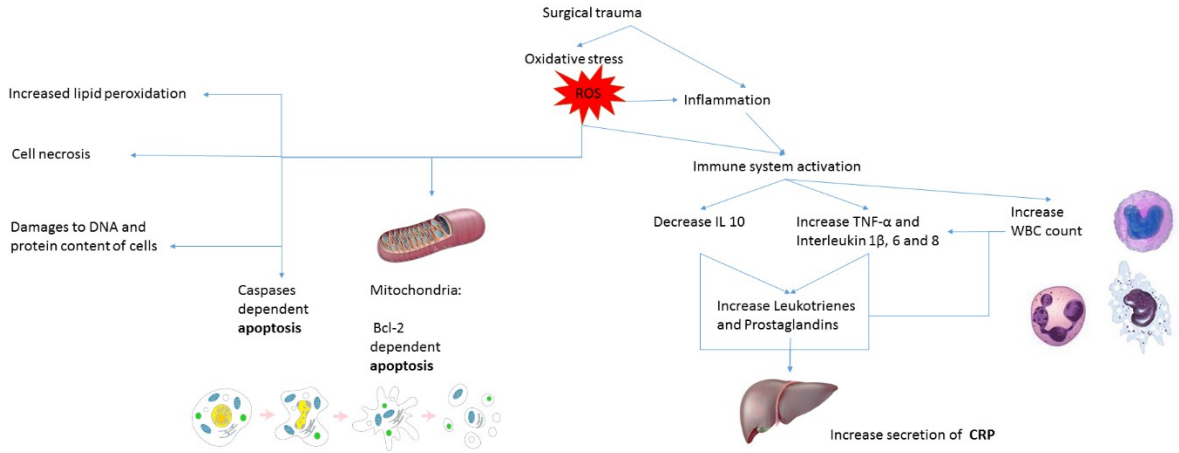
https://doi.org/10.37358/RC.20.1.7837

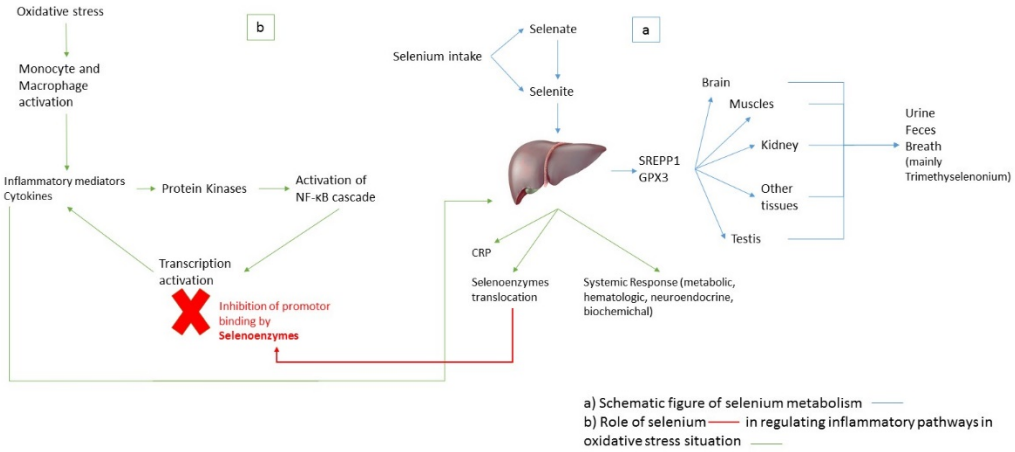
https://doi.org/10.37358/RC.19.10.7581

https://doi.org/10.37358/RC.19.6.7314

In the designation stage of the study, the research team established a review process through the past literature, followed by an expert panel which focused on the outcomes related to selenium availability, inflammation and oxidative stress status after the acute phase of stress caused by major GI surgeries receiving placebo infusion/ selenium supplementation within the next 5-10 days. In the current study with the research input of 2 sub-specialists of PICU, one sub-specialist of NICU, one immunologist, and 3 clinical nutritionists a conclusion is driven which suggests none of these classical markers including fibrinogen, erythrocyte sedimentation rate, ferritin, neutrophil-to-lymphocyte ratio thorough the determined dose and short period of placebo infusion/ selenium supplementation would illustrate changes in oxidative stress levels in PICU cases (9-12).

The following pictures, are taken from our accepted review article entitled “The Beneficial Anti-inflammatory and Anti-oxidative Effects of Selenium Supplementation in Critically Ill Post-surgical Pediatric Patients “ (13). In this diagram, the most specific and selenium related inflammatory and oxidative pathways activated following the acute phase of stress caused by major surgeries are demonstrated. As it is shown, they are different from the classical inflammatory markers and oxidative stress indices following chronic inflammatory diseases such as obesity and thrombocytopenia.



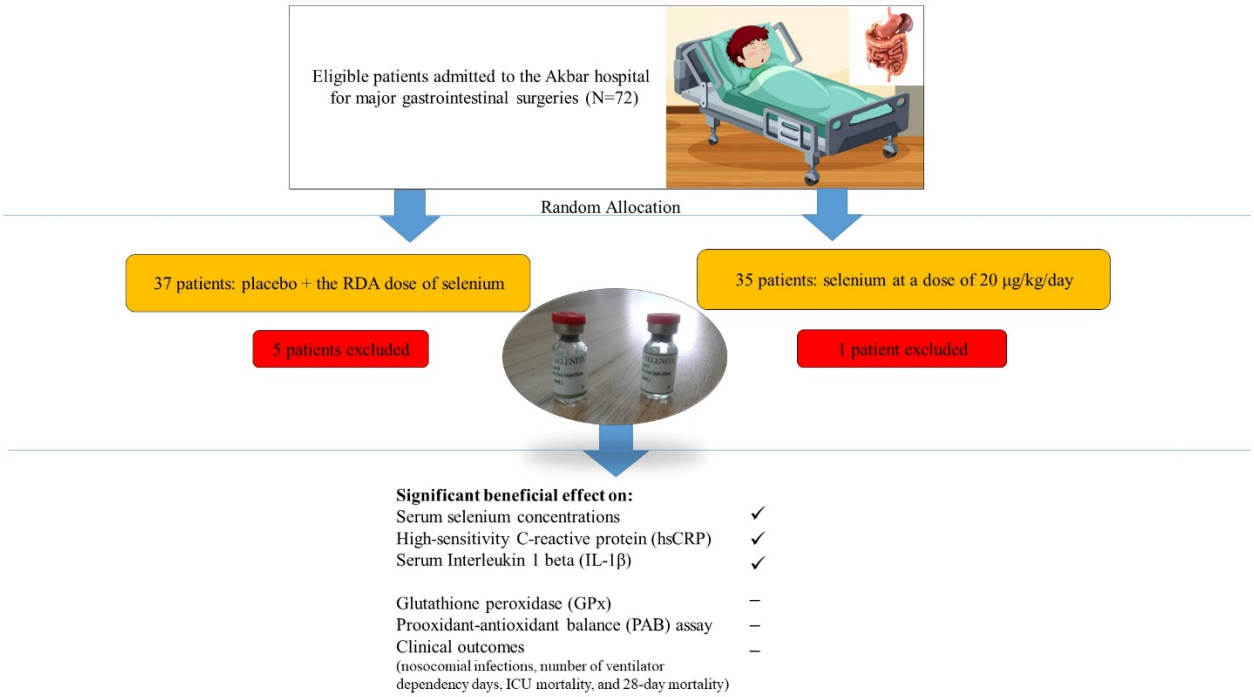


• *It is not completely clear to me whether the subjects received other vitamins/minerals as well. Vitamin C and vitamin E are potent antioxidants that also reduce the levels of oxidative stress and contribute to the prevention of infections. Please check:*
https://www.hindawi.com/journals/omcl/2014/158135/
https://doi.org/10.37358/RC.19.2.6977

As we have mentioned above, and in the manuscript: “All the patients were visited and monitored daily by clinical nutritionists. Moreover, not receiving concomitant supplementations (e.g., vitamin C, vitamin E, beta-carotene, zinc, copper, chromium, and manganese) were also monitored by the clinical nutritionists.”

• *I think the manuscript would benefit from a graphical abstract or a colourful figure describing the possible mechanisms of action of selenium as concluded from this randomized clinical trial.*

Amendments are done according to your request and a graphical abstract is presented as below:



4. Correct referencing and citations

The references are cited correctly and this section is arranged in accordance with the journal's guidelines.

Many thanks for your consideration.

5. Correct and proper English writing

The level of English is adequate. Maybe a spellcheck using the free version of Grammarly would be useful.

We applied this comment and asked a professional English-speaking colleague in the United Kingdom, who revised the final manuscript.

Reviewer 3:

The authors investigated the effects of high-dose selenium supplementation on oxidativestress and inflammatory markers in critically ill children after gastrointestinal surgery, which is a novel and

important subject. The paper is generally very good. The introduction provided sufficient background and logic behind the study. The study design and methods are well detailed. The results are provided in organized way. The discussion properly explained the results of this study as well as comparison with other studies. The references are adequate and recent. The paper is well-written with good language and structure.

Many thanks for your consideration, it would be our honor to hear these statements.

1. Bechard L, Ziegler J, Duggan C. Is Energy Expenditure of Infants Predictable After Surgery?A Review of the Evidence2010. 170-6 p.
2. Acar-Tek N, Agagunduz D, Celik B, Bozbulut R. Estimation of Resting Energy Expenditure: Validation of Previous and New Predictive Equations in Obese Children and Adolescents. Journal of the American College of Nutrition. 2017;36(6):470-80.
3. Marra M, Montagnese C, Sammarco R, Amato V, Della Valle E, Franzese A, et al. Accuracy of Predictive Equations for Estimating Resting Energy Expenditure in Obese Adolescents. The Journal of Pediatrics. 2015;166(6):1390-6.e1.
4. Broman M, Lindfors M, Norberg A, Hebert C, Rooyackers O, Wernerman J, et al. Low serum selenium is associated with the severity of organ failure in critically ill children. Clinical nutrition (Edinburgh, Scotland). 2018;37(4):1399-405.
5. Aggarwal R, Gathwala G, Yadav S, Kumar P. Selenium supplementation for prevention of late-onset sepsis in very low birth weight preterm neonates. Journal of tropical pediatrics. 2016;62(3):185-93.
6. Dao DT, Anez-Bustillos L, Cho BS, Li Z, Puder M, Gura KM. Assessment of Micronutrient Status in Critically Ill Children: Challenges and Opportunities. Nutrients. 2017;9(11):1185.
7. Leite HP, Nogueira PCK, Iglesias SB, Oliveira SV, Sarni ROS. Increased plasma selenium is associated with better outcomes in children with systemic inflammation. Nutrition. 2015;31(3):485-90.
8. Gärtner R. Selenium and thyroid hormone axis in critical ill states: An overview of conflicting view points. Journal of Trace Elements in Medicine and Biology. 2009;23(2):71-4.
9. Paruk F, Chausse JM. Monitoring the post surgery inflammatory host response. Journal of Emergency and Critical Care Medicine. 2019;3.
10. Sapin F, Biston P, Piagnerelli M. Predictive value of C-reactive protein in critically ill patients after abdominal surgery. Clinics. 2017;72:23-9.
11. Xiao Z, Wilson C, Robertson HL, Roberts DJ, Ball CG, Jenne CN, et al. Inflammatory mediators in intra-abdominal sepsis or injury – a scoping review. Critical Care. 2015;19(1):373.
12. Yamakawa K, Matsunaga M, Isowa T, Kimura K, Kasugai K, Yoneda M, et al. Transient responses of inflammatory cytokines in acute stress. Biological psychology. 2009;82:25-32.
13. Roudi F, Zakerian M, Ranjbar G. The Beneficial Anti-inflammatory and Anti-oxidative Effects of Selenium Supplementation in Critically Ill Post-surgical Pediatric Patients. Journal of Nutrition,Fasting and Health. 2020;In press(In press):-.

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) 11 Apr 2020

Dear AE,
The authors have significantly improved the quality of the paper after addressing the suggestions of the peer-reviewers. I believe the manuscript can be accepted in this form.
Thanks.

REFEREE: Reviewer | **Revision** (1) 11 Apr 2020

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

Mandana Rafeey: Associate Editor | **Revision** (1) 13 Apr 2020

Dear EIC,
I believe the manuscript can be accepted in this form.
Thanks.

REFEREE: EIC | **Revision** (1) 14 Apr 2020

Dear Authors,
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.