OPEN PEER REVIEW

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Iranian Journal of Pediatrics
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Peer Review Report for "Glutamine Supplementation Reduced Fasting Levels of High-Sensitivity C-Reactive Protein in Hospitalized Children with Acute Respiratory Infection: A Randomized Controlled Trial"

Author(s): Reza Alipanah-Moghadam, Manuchehr Barak, Reza Mohammadi, Ali Nemati, Vahideh Aghamohammadi, Mahsa Mohajeri, Elahe Mohammadi

Review Timeline:

Submit Date:	19 Jan 2022
Revised Date:	8 Mar 2022
Accepted Date:	10 Mar 2022

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) 23 Jan 2022

Dear AE,
The manuscript "Glutamine Supplementation Reduced Fasting Levels of hs-CRP in Hospitalized
Children with Acute respiratory infection" has been organized and written well. However, there are some points that should be addressed before its publication.
Title:
1. Study must be identified as "randomized controlled trial", in the title.
Abstract:
2. We are not allowed to use any abbreviations without first definitions (in abstract and text).
Methods:
3. This section is weak. It needs revision.
4. Time and duration of data collection should be stated.

5. Why did you decide to supplement for 5 days? Has any documents about the efficacy of 5 days Gln supplementation on antioxidants and inflammatory markers?
6. Nutrition intakes and medicine treatments as main confounders could affect intervention results. If possible, investigate the relation of these factors as confounders with the study's outcomes.
6. How did you calculate the sample size? Which formula? Explain it.
7. Who was blinded in the study? also please describe the method used to the blind of intervention.
Result:
8. Make clear which confounders (biochemical baseline values) were adjusted and why they were included.
9. Due to the differences at baseline of hs-CRP between the groups, please adjust the study outcomes according to baseline hs-CRP, and also, it should be noted in the result.
10. It suggested that mean change (before and after within groups) compare between groups.
11. Continuous quantitative variables should be described as (parametric) mean (standard deviation) and (non-parametric) median (quartile).
Discussion:
12. In the discussion section, Line 3, it was written " mean of IL-1β, TNF-α, and hs-CRP were
significantly reduced in the Gln group" however, the results of the study do not support this claim.
Thanks.

REFEREE: Reviewer | **Revision** (0) 25 Jan 2022

Dear AE,
An article entitled "Glutamine Supplementation Reduced Fasting Levels of hs-CRP in Hospitalized Children with Acute respiratory infection" was reviewed.
The manuscript is well written. There are some minor revisions mentioned below:
Abstract:
- It is recommended to mention significant values for all cases in the results section
Introduction:
- Old sources have been used to link glutamine to inflammatory markers. It is suggested to use more up-to-date articles in this field
- It is better to explain whether other studies in this field have been performed in humans, whether adults or children
If not, at least it should be mentioned as a comparative advantage, which is the first study in this field
Method:
- In the methods section, on what basis is the dose and duration selected?
- The method of determining the sample size is not seen in the text. It is suggested that this case be mentioned
- The selection of statistical methods for analysis is well done
Results:
- The results are well reported

Discussion:

- It is recommended that the reasons for the results that are not meaningful be explained in some detail in the discussion. Simply mentioning parallel studies does not strengthen the discussion
- It should be noted what performance or benefits the results of this study have in the clinical practice.

Thanks.

REFEREE: Associate Editor | **Revision** (0) 25 Jan 2022

Dear EIC,

The manuscript has been assessed by the journal's reviewers and we regret to inform you that present manuscript needs to major revision according to reviewer's comments.

Thanks.

REFEREE: EIC | **Revision** (0) 29 Jan 2022

Dear Authors,

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.

Manuscript Title: **Glutamine Supplementation Reduced Fasting Levels of hs-CRP in Hospitalized Children with Acute respiratory infection: A Randomized Controlled Trial**

Manuscript ID: **122049**

Response-to-review table

****All revised sections are highlighted in the manuscript.**

Reviewer 1	
Comments to the Author	**Authors, s Responses to the Reviewer**
An article entitled "Glutamine Supplementation Reduced Fasting Levels of hs-CRP in Hospitalized Children with Acute respiratory infection" was reviewed. The manuscript is well written. There are some minor revisions mentioned below:	Thanks for your helpful and excellent suggestions.
Abstract: - It is recommended to mention significant values for all cases in the results section	We included significant values in the results section. Page 1 , line 14
Introduction: - Old sources have been used to link glutamine to inflammatory markers. It is suggested to use more up-to-date articles in this field - It is better to explain whether other studies in this field have been performed in humans, whether adults or children. If not, at least it should be mentioned as a comparative advantage, which is the first study in this field.	-We used more up-to-date articles to link glutamine to inflammatory markers. Page 2, line 47 and page 11, line 242-257. -We mentioned that this study is the first to evaluate the effects of Gln supplementation on serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), high-sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA), and total antioxidant capacity (TAC) in hospitalized children with ARI. Page3, line 62
Method: - In the methods section, on what basis is the dose and duration selected?	- We selected the dose and duration according to the following studies (page 12, references 37-39): Kumar S, Kumar R, Sharma SB, Jain BK. Effect of oral glutamine administration on oxidative stress, morbidity and mortality in critically ill surgical patients. Indian Journal of Gastroenterology. 2007;26(2):70. Javanamani R, Nakhostin-Roohi B. The Effect of One-week Glutamine Supplementation on Oxidative Stress Indices in Healthy Young Men. Journal of Ardabil University of Medical Sciences. 2015;15(1):83-9. Jordan I, Balaguer M, Esteban ME, Cambra

- The method of determining the sample size is not seen in the text. It is suggested that this case be mentioned - The selection of statistical methods for analysis is well done.	FJ, Felipe A, Hernández L, et al. Glutamine effects on heat shock protein 70 and interleukines 6 and 10: Randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children. Clinical nutrition. 2016;35(1):34-40. - The sample size was determined based on serum MDA as the primary outcome obtained from our previous study (reference 23) :Nemati A, Alipanah-Moghadam R, Molazadeh L, Baghi AN. The effect of glutamine supplementation on oxidative stress and matrix metalloproteinase 2 and 9 after exhaustive exercise. Drug design, development and therapy. 2019;13:4215.). The sample size was computed using the following formula: N= [(Z1-α/2) + (Z1-β)]2 × (δ12 +δ2 2)/(μ2 - μ1)2] (α = 0.05 and β=0.2). Considering a withdrawal, 22 subjects were recruited. Page 4, line 86-91.
Results: - The results are well reported	Thanks for your helpful and excellent comments.
Discussion: - It is recommended that the reasons for the results that are not meaningful be explained in some detail in the discussion. Simply mentioning parallel studies does not strengthen the discussion - It should be noted what performance or benefits the results of this study have in the clinical practice.	-We presume that the diversities between the conducted studies may be related to various patient groups, dose, and the duration of Gln administration. Page 9, line 192-194. - We added these sentences to discussion section: Since the elevation of hs-CRP and other inflammatory biomarkers are related to pneumonia in children, a decrease of inflammatory biomarkers through safe supplements such as Gln along with medicine can help to cure ARI and infectious morbidity rates reduction. Page 8, line 169-172.
Reviewer 2	
Comments to the Author	**Authors, s Responses to the Reviewer**
The manuscript "Glutamine Supplementation Reduced Fasting Levels of hs-CRP in Hospitalized Children with Acute respiratory infection" has been organized and written well. However, there are some points that should be addressed before its publication.	Thanks for your helpful and excellent suggestions.

Title: 1. Study must be identified as "randomized controlled trial", in the title.	1-We included “randomized controlled trial” in the title. Page 1, line 2
Abstract: 2. We are not allowed to use any abbreviations without first definitions (in abstract and text).	2-We described any abbreviations in the first use in the whole text. Page 1, line 9 and 11-13
Methods: 3. This section is weak. It needs revision. 4. Time and duration of data collection should be stated. 5. Why did you decide to supplement for 5 days? Has any documents about the efficacy of 5 days Gln supplementation on antioxidants and inflammatory markers? 6. Nutrition intakes and medicine treatments as main confounders could affect intervention results. If possible, investigate the relation of these factors as confounders with the study's outcomes. 6. How did you calculate the sample size? Which formula? Explain it.	3- we have edited this section. Page 4 line 81 and 86-91- Page 5, line 94-96- Page 6, line 127. 4- We stated the time and duration of data collection. Page 4, line 81. 5- We selected the dose and duration according to the following studies (page 12, references 37-39): Kumar S, Kumar R, Sharma SB, Jain BK. Effect of oral glutamine administration on oxidative stress, morbidity and mortality in critically ill surgical patients. Indian Journal of Gastroenterology. 2007;26(2):70. Javanamani R, Nakhostin-Roohi B. The Effect of One-week Glutamine Supplementation on Oxidative Stress Indices in Healthy Young Men. Journal of Ardabil University of Medical Sciences. 2015;15(1):83-9. Jordan I, Balaguer M, Esteban ME, Cambra FJ, Felipe A, Hernández L, et al. Glutamine effects on heat shock protein 70 and interleukines 6 and 10: Randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children. Clinical nutrition. 2016;35(1):34-40. 6-lack of nutritional intake evaluation was one of the limitations of the present study and we added this sentence to the last part of discussion (page 9, line 197). Also, all participants had received the same medicine, then we did not adjust them. 6-The sample size was determined based on serum MDA as the primary outcome obtained from our previous study (reference

7. Who was blinded in the study? also please describe the method used to blind of intervention	23):Nemati A, Alipanah-Moghadam R, Molazadeh L, Baghi AN. The effect of glutamine supplementation on oxidative stress and matrix metalloproteinase 2 and 9 after exhaustive exercise. Drug design, development and therapy. 2019;13:4215.). The sample size was computed using the following formula: N= [(Z1-α/2) + (Z1-β)]2 × (δ12 +δ2 2)/(μ2 - μ1)2] (α = 0.05 and β=0.2). Considering a withdrawal, 22 subjects were recruited. Page 4, line 86-91. 7-A member of the research team who was not involved in assessing the outcome of the study was responsible for generating the allocation sequence and allocated participants to the sequence (page 5, line 94-96) and the data analyst was blinded after assignment to interventions. Page 6, line 127.
Result: 8. Make clear which confounders (biochemical baseline values) were adjusted and why they were included. 9. Due to the differences at baseline of hs-CRP between the groups, please adjust the study outcomes according to baseline hs-CRP, and also, it should be noted in the result. 10. It suggested that mean change (before and after within groups) compare between groups. 11. Continuous quantitative variables should be described as (parametric) mean (standard deviation) and (non-parametric) median (quartile).	8 and 9- We considered TNF-α, IL-1β, hs-CRP, MDA, and TAC baseline values as confounders according to our statistical specialist. Page 6, line 137. 10- We reported the mean difference within groups. Page 14, table 2 11- We reported continuous quantitative variables as mean (standard deviation) and non-parametric as median (percentile) according to your valuable suggestion. Page 13 and 14, table 1 and 2.
Discussion: 12. In the discussion section, Line 3, it was written " mean of IL-1β, TNF-α, and hs-CRP were significantly reduced in the Gln group" however, the results of the study do not support this claim.	12- As it is mentiond in last paragraph of the results section (page 7, line 147-154) and also in table 2 (page 14), the serum values of IL-1β, TNF-α, and hs-CRP significantly decreased in the Gln group ($p<0.05$) at the end of the intervention, but in comparison with placebo group the changes were not significant.

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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) 21 Feb 2022

Dear AE,
Comments to the Author:
The great effort in improving the manuscript is highly appreciated. Thank you for presenting this manuscript, so the manuscript seems appropriate for publication.
However, I have a few comments.
1. Page 6, lines 97-98, It suggested that the documents of dose and duration of supplementation as references be cited.
2. Page 6, line 137, Please include biochemical variable names as confounding variables (TNF-, IL-1, hs-CRP, MDA, and TAC).
3. Why did you not measure appetite as the outcome at the end of the study?
4. Page 7, line 158, the within-group comparison in RCTs is not a valuable result that noted in the first paragraph of the discussion and it is possible to misunderstanding. Because the goal of RCT is to compare the effects of intervention between study groups.
5. Discussion: It was advised that the mechanism of therapeutic effects of Gln on hs-CRP reduction be noted.
Thanks

REFEREE: Reviewer | **Revision** (1) 23 Feb 2022

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

REFEREE: Associate Editor | **Revision** (1) 23 Feb 2022

Dear EIC,
The manuscript has been assessed by the journal's reviewers and we regret to inform the authors that the present manuscript needs minor revision according to the reviewer's comments.
Thanks.

REFEREE: EIC | **Revision** (1) 25 Feb 2022

Dear Authors,

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.

Manuscript Title: **Glutamine Supplementation Reduced Fasting Levels of hs-CRP in Hospitalized Children with Acute respiratory infection: A Randomized Controlled Trial**

Manuscript ID: **122049**

Response-to-review table

****All revised sections are highlighted in the manuscript.**

Reviewer 1	
Comments to the Author	**Authors, s Responses to the Reviewer**
The great effort in improving the manuscript is highly appreciated. Thank you for presenting this manuscript, so the manuscript seems appropriate for publication. However, I have a few comments.	Thanks for your helpful and excellent suggestions.
1. Page 6, lines 97-98, It suggested that the documents of dose and duration of supplementation as references be cited.	We included references for the sentences about the dose and duration of supplementation. (page 5, Participants and Intervention section)
2. Page 6, line 137, Please include biochemical variable names as confounding variables (TNF-, IL-1, hs-CRP, MDA, and TAC).	We included biochemical variable names as confounding variables (TNF-, IL-1, hs-CRP, MDA, and TAC) in the statistical analysis. (page 6, Statistical analysis section)
3. Why did you not measure appetite as the outcome at the end of the study?	Our primary aims were the evaluation effects of Gln supplementation on serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), high-sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA), and total antioxidant capacity (TAC) in hospitalized children with ARI, then we did not measure appetite at the end of study.
4. Page 7, line 158, the within-group comparison in RCTs is not a valuable result that noted in the first paragraph of the discussion and it is possible to misunderstanding. Because the goal of RCT is to compare the effects of intervention between study groups.	We eliminated the mentioned sentences from the discussion. (page 7, Discussion section)
5. Discussion: It was advised that the mechanism of therapeutic effects of Gln on hs-CRP reduction be noted.	We included sentences regarding the mechanism of therapeutic effects of Gln on inflammatory markers. (page9, Discussion section)
Reviewer 2	
Comments to the Author	**Authors, s Responses to the Reviewer**
All comments have been made and corrections are acceptable.	Thanks for your helpful and excellent suggestions.

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: Associate Editor | **Revision** (2) 9 Mar 2022

Dear EIC,
The great effort in improving the manuscript is highly appreciated. Thanks to the authors for presenting this manuscript. I totally appreciate the efforts that have been done by the authors in conducting this interesting study.
Thanks

REFEREE: EIC | **Revision** (2) 10 Mar 2022

Dear Authors,
Thank you for submitting your manuscript to Iran J Pediatr for consideration for publication. The third round of peer review of your manuscript is complete. At this time, your manuscript is acceptable for publication.
Thanks.