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OPEN PEER REVIEW

Efficacy of Vitamin D as Adjuvant Therapy for Treatment of Hospitalized Children with COVID-19: A Randomized Clinical Trial

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1 Original submission

2 comments · 8 Jul 2023 – 8 Jul 2023

Associate Editor

MAJOR REVISION 8 Jul 2023

Dear EIC,
I thank the authors and express my appreciation to the researchers. The manuscript is a valuable piece of research. But some revisions are needed. The authors should revise it based on the comments. Also, minor changes should be made in the ABSTRACT:

Background:

The background provides a brief rationale for the study, highlighting the role of vitamin D in the immune system and the association between low serum levels of vitamin D and COVID-19. However, it would be helpful to provide more context and cite relevant studies to support these statements.
The objective of the study should be explicitly stated in the background section of the ABSTRACT.
Methods:

The methods section briefly describes the study population and the randomization process. However, more details are needed regarding the inclusion and exclusion criteria, such as age range, severity of illness, and any specific comorbidities.
The intervention and control groups are mentioned, but it would be helpful to provide more information on the specific vitamin D regimen used in the intervention group (e.g., dose, frequency, duration).
The outcome measures mentioned (time to recover from fever and respiratory distress, length of hospitalization) are appropriate. However, it would be beneficial to provide the statistical methods used for the analysis.
Results:

The results section provides information on the number of patients evaluated and the initial differences observed between the intervention and control groups. However, it would be helpful to provide more specific data, such as the mean age of the patients, the actual numbers of patients with fever in each group, and the mean duration of hospitalization.
The p-values for the comparisons between the groups are mentioned, but it would be beneficial to provide the effect sizes or confidence intervals to better understand the magnitude of the differences observed.
Conclusion:

The conclusion states that the administration of vitamin D at a dose of 1000 mg per day did not show any significant efficacy in the recovery of children with COVID-19. However, it is important to note that the standard unit for measuring vitamin D is typically IU (international units), not mg (milligrams). Clarification is needed on the unit of measurement used in the study.
The suggestion for further studies investigating high-dose vitamin D supplementation is appropriate. However, it would be beneficial to provide a brief rationale for why higher doses of vitamin D may be worth investigating.
Language and Clarity:

The overall language and clarity of the abstract are good. However, there are some grammatical errors and awkward sentence structures throughout the text that should be addressed.
Missing Information:

Additional information is needed regarding the specific characteristics of the study population, such as age range and severity of illness.

It would be helpful to mention the duration of the study and whether any ethical approval or informed consent was obtained.

Editor-in-Chief MAJOR REVISION 8 Jul 2023

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

> Reviewers' Comments:

Thanks to the esteemed referees, the following items have been corrected and highlighted in the text:

Reviewer 1:

BACKGROUND:

1- It needs revision, totally. The first three paragraphs must be summarized and deleted. This section is not lecture notes. The introduction should include a better representation of the main rationale of the study (Efficacy of vitamin D in the treatment of COVID-19) and emphasis on the limitations of previous studies.

Respnce: The necessary correction was made and the first three paragraphs were summarized in one paragraph.

2- In paragraph 4, other new functions of vitamin D should be expressed. In fourth paragraph, it is suggested that “vitamin D functions” should be expressed in more detail and one or more sentences must be noted about this issue. For example you note: [Throughout the body, vitamin D receptors are present in skeletal and smooth muscles as well as in the bladder. Vitamin D studies shows that it (this vitamin) is involved in disturbances other than bone metabolism. In the children, it is contributed with diverse disorders such as asthma, infection of respiratory tract, insulin resistant, metabolic and autoimmune syndrome, infertility, urinary tract infection, over active bladder syndrome, pelvic floor muscle disorder and enuresis.] You should be mentioned to this valuable and new article in your references: Siroosbakht S. Are Vitamin D Levels Linked to Primary Monosymptomatic Nocturnal Enuresis in Children? Six Years of Experience about a Controversy in Medicine: A Case-Control Study. Iran J Pediatr. 2023;33(3):e133755

Re: Necessary corrections were made and new points were also included in the study.

Objects:

3. The first sentence was repetitive. Pl deletes it.

Re: This sentence was deleted.

Methods:

4. Date of study?

Re: The study date was added in the method.

5. What was sampling methods?

Re: With respect, the sampling method is random block, which is fully explained in the second paragraph.

6. How did you calculate the sample size? Which formula did you use? Number of subjects were inadequate and very low.

Re: According to limited the number of cases suffering from Coronavirus disease 2019 last year in the hospital and due to the vaccination low and prevalence of patients in recent year, in consultation with the statistics professor, we determined the number of 20 people in each group. Of course, we were able to increase the number to thirty people. Samples include hospitalized children suffering from Coronavirus disease 2019 in hospital that have 3 months to 14 years of age.

7. Exclusion and inclusion criteria were incomplete such as intake of vitamin D, liver disease, celiac and anticonvulsant drugs that influence the vit D status of subjects.

Re: We considered not taking vitamin D or effective drugs including anticonvulsants or chemotherapy in the study. Although, unfortunately, only chemotherapy was mentioned in the article, which was corrected according to the guidance of the honorable referee. In addition, inclusion and exclusion criteria were given in the first paragraph.

8. Inclusions and exclusions criteria must be mention to first paragraph then after, eligible and allocated participants were noted (with number, exact and clearly).

Re: Necessary corrections were made and new points were also included in the study.

9. Eligible and allocated participants were noted in text (with number, briefly and clear). Finally, the number of subjects analyzed should be stated.

RE: Thanks to your valuable guidance, all the desired items have been added in the text.

10. How many subjects were assessed for eligibility? And then how many subjects were allocated?

RE: Thanks to your valuable guidance, all the desired items have been added in the text.

11. Did you Lost to follow-up?

RE: We did not have a case of missing in the follow-up and finally 30 patients in each group were analyzed, all the desired items have been added in the text.

12. How you prescribe soft gel of vit D to infant less than 1 yr age? pl descript it .

Re: To administer vitamin D in infants under one year old, the content of the soft gel was drawn with a syringe and mixed with a little milk or yogurt.

13. What were basic treatments for the subjects? Pl define and expressed those, precise and clear (in each groups).

Re: Necessary treatments were carried out according to the clinical condition of each patient according to national guidelines, and the only difference considered was the administration of vitamin D in the intervention group.

14. There are many important confounders in this regards such as age, gender, BMI, nutritional status of subjects, complementary intake, levels of micronutrients in your subjects, history of allergy, family history, endocrine, metabolic, renal disorders and anomalies, level of education of parents, and any physical abnormality and so on. Furthermore, many confounders about these such as genetic, age, gender, drinking and so on. But I did not see any investigation for relation of these important factors with status of subjects.

Re: With respect, there are such confounding factors in all interventional studies, and unfortunately, all these cases cannot be included in the study. With all this, the random assignment of patients to two groups significantly reduces the effect of these factors on the final result. I hope this explanation is convincing for the esteemed referee.

15. Describe statistical methods, used to control for confounding. Control of confounders is an important point in this study.

Re: We compared the evaluable confounding factors in two groups. As mentioned in the article: “The two groups were similar in terms of age, gender, duration of disease and severity of disease and no significant difference was observed.”

16. The definition of disease severity need references. Add it in your references (line 176).

Re: The following reference was added to the article's references: 20. National Committee for Children's Covid-19. Coronavirus Disease 2019 (COVID-19) Diagnosis and Treatment Guideline in children and infants. Ministry of Health, Treatment and Medical Education of the Islamic Republic of Iran; seventh edition 2022. 109 pages.

Results:

17. Many sentences in first and second paragraphs were repetitive. Pl merges those.

Re: The repetitive sentences were deleted.

18. Many underlying diseases in the children were confounders and may be influence the vit D intake and or response to basic treatment of COVID -19 such as gastrointestinal diseases, History of intestinal surgery, kidney Diseases and so on.

Re: As can be seen, existing underlying diseases usually do not affect vitamin D absorption or levels, and in addition, there were no significant differences between the two groups. The inclusion and exclusion criteria have been determined based on previous relevant studies and underlying diseases that have an effect on the absorption or level of vitamin D, and according to the explanations of the above items, they were more clearly expressed according to your guidance. It is hoped that the explanation will be convincing for the esteemed referee.

19. Again, Exclusion and inclusion criteria were incomplete. Pl mentions the aforementioned comments in methods section. It must be excluded the subjects with underlying diseases and analysis again.

Re: Please refer to the answer above.

Discussion:

20. In first paragraph, the authors avoid the finding that no significant. This paragraph needs revision.

Re: The paragraph was revised and highlighted.

21. I see limitation of study. However, recommendations were not seen. Limitation and recommendation should be mentioned in the last paragraph of discussion and in last paragraph any gap, question, hypothesis or comment should be declared.

Re: Necessary recommendations were provided based on the limitations of our study.

Conclusion:

22. It was not justified. the finding that no significant must be deleted. It should be mentioned according to significant and main finding.

Re: The necessary correction was made.

References:

23. Those should be noted based on journal rules. (pl see the number of authors in your references).

Re: The number of authors in the references was also modified.

Thank you

> Associate Editor's Comments:

Background:

The background provides a brief rationale for the study, highlighting the role of vitamin D in the immune system and the association between low serum levels of vitamin D and COVID-19. However, it would be helpful to provide more context and cite relevant studies to support these statements.

The objective of the study should be explicitly stated in the background section of ABSTRACT.

Re: Necessary corrections were made and new points were also included in the Background of the study.

Methods:

The methods section briefly describes the study population and the randomization process. However, more details are needed regarding the inclusion and exclusion criteria, such as age range, severity of illness, and any specific comorbidities.

The intervention and control groups are mentioned, but it would be helpful to provide more information on the specific vitamin D regimen used in the intervention group (e.g., dose, frequency, duration).

The outcome measures mentioned (time to recover from fever and respiratory distress, length of hospitalization) are appropriate. However, it would be beneficial to provide the statistical methods used for the analysis.

Re: All the corrections desired by the dear editor were included and highlighted in the Methods section of article.

Results:

The results section provides information on the number of patients evaluated and the initial differences observed between the intervention and control groups. However, it would be helpful to provide more specific data, such as the mean age of the patients, the actual numbers of patients with fever in each group, and the mean duration of hospitalization. The p-values for the comparisons between the groups are mentioned, but it would be beneficial to provide the effect sizes or confidence intervals to better understand the magnitude of the differences observed.

Re: With respect, all relevant information is included in Tables 2, 3 and 4.

Conclusion:

The conclusion states that the administration of vitamin D at a dose of 1000 mg per day did not show any significant efficacy on the recovery of children with COVID-19. However, it is important to note that the standard unit for measuring vitamin D is typically in IU (international units), not mg (milligrams). Clarification is needed on the unit of measurement used in the study.

Re: Unfortunately, the milligram case in the summary was a typo that was corrected. Thanks to the accuracy of the dear editor.

The suggestion for further studies investigating high-dose vitamin D supplementation is appropriate. However, it would be beneficial to provide a brief rationale for why higher doses of vitamin D may be worth investigating.

Re: This item was also added in the suggestions section at the end of the discussion.

Language and Clarity:

The overall language and clarity of the abstract are good. However, there are some grammatical errors and awkward sentence structures throughout the text that should be addressed.

Re: Grammatical re-editing of the text was also done.

Missing Information:

Additional information is needed regarding the specific characteristics of the study population, such as age range and severity of illness.

It would be helpful to mention the duration of the study and whether any ethical approval or informed consent was obtained.

Re: Respectfully, the desired items are mentioned in the text or in the tables, including the severity of the disease in table one. The age range and study period were also added.

Thank you again to the esteemed referees and dear editor.

2 Revision 1

2 comments · 23 Jul 2023 – 23 Jul 2023

Associate Editor

ACCEPT 23 Jul 2023

Dear EIC,
I reviewed the manuscript again. The great effort in improving the manuscript is highly appreciated.
The authors have addressed all comments.
Thank you

Editor-in-Chief

ACCEPT 23 Jul 2023

Dear Author,
Thank you for correcting pitfalls and answering questions.