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OPEN PEER REVIEW

Comparative Effects of Valganciclovir and Ganciclovir on the Congenital Cytomegalovirus Infection and Hearing Loss: A Randomized Controlled Trial

Lili Yang, Aijuan Qiu, Jing Wang, Zhaojun Pan

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

4 comments · 16 Sep 2021 – 8 Oct 2021

Referee 1 Reviewer

MAJOR REVISION 16 Sep 2021

Dear Author
Please remove the title "objectives" from the background.
In Methods, you should not write the results.
Please check the analysis method. I think you have to write paired t-test and independent t-test.
In the results, just explain the parts that are not in the table.
Can a 31-week-old baby tolerate oral medication, and is its absorption from the gut reliable?

Elahe Norouzi Reviewer

MAJOR REVISION 20 Sep 2021

Although the subject of the study is not novel and the effectiveness of Valganciclovir in the treatment of congenital CMV infection has been accepted for a decade, the authors' work is appreciated if it has been performed in their setting for the first time.
The manuscript needs major revision, as detailed below:
- The title and running title should be edited; the running title may be changed from “Ganciclovir on the curative effect and hearing”!! to “curative effect of Valganciclovir in CMV infection”.
- Abstract: The background section is not sufficient or relevant. In the first line of the results, after “no statistical significant”, the word “difference” should be added.
- Keywords should be changed according to the MeSH browser to: newborn, cytomegalovirus, Ganciclovir, Valganciclovir, infections
- Background: What is the last word? “Newonates”?!!! Please correct it wherever it appears in the manuscript.
- Method: What is the study design? Clinical trial? Case-control? What was the total population of neonates from which 48 were enrolled in this study?
- Method: You mentioned that “no ROP” is one of your inclusion criteria, and all of your cases were included in the study in the first 15 days of life, so how did you assess ROP before 28 days? Retinopathy of prematurity is an exclusion criterion, not an inclusion criterion.
- Method: How did you evaluate “being allergic to therapeutic”? Or do you mean anaphylaxis?

Ali Amanati Reviewer

MAJOR REVISION 27 Sep 2021

First, the Methods section. The treatment indication used in this study does not fully match AAP guidelines and international consensus recommendations for congenital CMV management (newborns with normal hearing and mild SNHL have been included). However, if the authors determine the characteristics of newborns who already have SNHL despite treatment, the results of the study may be useful. This includes the determination of the primary severity group of newborns who developed SNHL despite treatment. See http://dx.doi.org/10.1016/S1473-3099(17)30143-3 and American Academy of Pediatrics. [Cytomegalovirus] In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[289].
Second, the Methods section. The follow-up duration for monitoring SNHL (the main outcome) is short and is not in line with standard recommendations. See the American Academy of Pediatrics Bright Futures:

Guidelines for Health Supervision of Infants, Children, and Adolescents, 4th Edition, which recommends hearing testing at 4, 6, 9, 12, 15, 18, 24, and 30 months of age. This should be considered a study limitation.

Other shortcomings:
The title should be rewritten with better words.
Lines 11-12: the route of administration of VGCV and GCV is not specified.
Line 16: spell out "BAEP".
Line 46: remove "etc."
Lines 47-52: drug formulations are not specified. Specify oral versus intravenous formulations throughout the manuscript.
Line 49: remove this part: "Oral administration of this drug has low utilization rate and
50 is also accompanied by side effects such as fever and chills." The oral formulation of GCV is currently not in use.
Lines 51-52: remove this statement: "At present, for these 2 drugs, it is unclear which one is better for the symptoms of congenital CMV infection among newonates." Based on the AAP recommendation, both approaches (oral VGCV and intravenous GCV) are acceptable for the treatment of eligible CMV-infected neonates. See American Academy of Pediatrics. [Cytomegalovirus] In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[289].
Line 69-70: "symptoms" based on the 2015 5th International Congenital CMV Conference should be defined based on severity. A table should be provided to specify the diagnostic criteria considered in this study and the proportion of newborns in the case and observational groups meeting the diagnostic criteria from the 2015 5th International Congenital CMV Conference.
Line 84: define how the VGCV oral formulation is prepared for newborn infants.
Lines 121-124. This statement is not informative and should describe hearing loss improvement in each group in more detail, based on hearing loss severity. How many of those with severe and extremely severe SNHL improved, and by how much? How many of those with mild SNHL fully improved?
Line 274 (table-1): define "z-value" and "($\bar{x}\pm s$)".

Referee 2 Reviewer

REJECT 8 Oct 2021

Public Comments:

Ethics: This study is a clinical trial. No information was found about the registration of this study or its registration number.

Title:
The title and running title need revising.

Grammar correction is needed. The manuscript contains many grammatical errors.
Background:
"Line 47 and 48: GCV is a common broad-spectrum antiviral drug with high curative effects. It can treat symptoms due to CMV infection,"
Please be more specific. Replace the word "symptoms" with "manifestation" or a broader word to include signs and other sequelae of CMV infection.

Please correct the word "newonate" to "the neonate or newborn" throughout the document (>5 cases).

Methods:
Lines 99-100 (3) Comparison of hearing loss between the 2 groups during treatment by TEOAE hearing screening and BAEP
Please expand the acronyms at their first occurrence.

Line 81 Dose for the infusion was determined based on the body weight of 6mg/ml,
Correct 6mg/ml to 6 mg/kg?

Result:
The tables and results text should not repeat each other.

Discussion
Generally accepted facts should not be mentioned as results of this study. The discussion contains many basic science facts that are irrelevant to the principal argument of the study.
Lines 158-159: Hyperbilirubinemia is commonly known as jaundice clinically,
Hyperbilirubinemia is not another term for jaundice. However, they refer to a similar condition. Clinically, jaundice appears when bilirubin surpasses 2.5 mg/dl.

The limitation of the study should be addressed.

6. Conclusions
Conclusion: The conclusion should be drawn from the study's findings.

2

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:
Reviewer 1:
First, the Methods section. Treatment indication which used in this study is not fully matched with AAP guidelines and international consensus recommendations for congenital CMV management (newborns with normal hearing and mild SNHL have been included). However, if the authors determine the characteristics of newborns who already have SNHL despite treatment, the results of the study may be useful. This includes the determination of the primary severity group of newborns who have complicated with SNHL despite treatment. See, http://dx.doi.org/10.1016/S1473-3099(17)30143-3 and American Academy of Pediatrics. [Cytomegalovirus] In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[289].
Second, the Methods section. The follow-up duration for monitoring SNHL (the main outcome) is short and is not in line with standard recommendations. See, the American Academy of Pediatrics Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, 4th Edition, which recommends hearing testing at 4, 6, 9, 12, 15, 18, 24, and 30 months of age. This should be considered as a study limitation.
Other shortcomings:
The title should be rewritten with better words.
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Line 16: spell-out "BAEP"
Line 46: remove "etc."
Lines 47-52: drug forms is not determined. Determine oral versus intravenous formulation in the whole manuscript.
Line 49: remove this part: "Oral administration of this drug has low utilization rate and 50 is also accompanied by side effects such as fever and chills.", oral formulation of GCV currently is not in use.
Lines 51-52: remove this statement: "At present, for these 2 drugs, it is unclear which one is better for the symptoms of congenital CMV infection among newonates."; based on AAP recommendation both approaches (oral VGCV and intravenous GCV) are acceptable for the treatment of eligible CMV infected neonates. See, American Academy of Pediatrics. [Cytomegalovirus] In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[289].
Line 69-70: "symptoms" based on the 2015 5th International Congenital CMV Conference should be defined based on severity. A table should be provided for the determination of diagnostic criteria considered in this study and the proportion of newborns in the case and observational group meeting the diagnostic criteria from the 2015 5th International Congenital CMV Conference.
Line 84: define how VGCV oral formulation is prepared for newborn infants.
Lines 121-124. This statement is not informative and should be more descriptive based on hearing loss improvement in each group based on hearing loss severity. How many of those with severe and extremely severe SNHL improved and how much? How many of those with mild SNHL fully improved?
Line 274 (table-1): define "z-value" and "($\bar{x}\pm s$)"
Reply to Reviewer 1: Thank you very much for your pertinent and detailed comments

and suggestions. The indications used in this study may not fully match some of the international consensus, but we have made some more local adjustments for the indications in order to enrich the comprehensive study data. The title of this study has been revised in response to comments. Methods and dosages of VGCV and GCV have been added to the summary methods section. Some incorrect content has been removed. Table 2 was significantly modified to more detail the improvement of hearing symptoms in both groups.

Reviewer 2:
Although the subject of the study is not a novel work and the effectiveness of Valganciclovir is accepted in treatment of congenital CMV infection from one decade ago, the work of authors is appreciated if it is performed in their setting for the first time. The manuscript needs major revision, as it is mentioned subsequently:
- The title and running title should be edited; running title may be change from “Ganciclovir on the curative effect and hearing”!! to “curative effect of Valganciclovir in CMV infection”
- Abstract: background section is not sufficient and relevant. In first line of results, after “no statistical significant” the word “difference” should be added.
- Key words should be changed according to Mesh browser to: newborn, cytomegalovirus, Ganciclovir, Valganciclovir, infections
- Background: what is the last word? “Newonates”?!!! please correct it wherever it is in the whole manuscript.
- Method: what is the method of the study? Clinical trial? Case-control? How many neonates are the population of the study which 48 out of them enrolled this study?
- Method: you mentioned that “no ROP” is one of your inclusion criteria, and all of your cases included in the study in first 15 days of life, so, how you assessed ROP before 28 days? Retinopathy of prematurity is an exclusion criteria not an inclusion one.
- Method: how you evaluated “being allergic to therapeutic”? or do you mean anaphylaxis?
Reply to Reviewer 2: Thank you very much for your questions and comments. The title, keywords and abstract of this paper have been revised. The design method of this study has been added to the methodology section. The inclusion criteria were modified according to the actual situation. The "allergy" referred to in this method refers to the condition in which the newborn is allergic to the Ganciclovir or Valganciclovir.

Reviewer 3:
Dear Author
please remove Title "objectives" in background.
In Methods you should not write the results
Please check analysis method i think you have to write paired t-test and independent t-test
In results just explain the parts that are not in the table
can a 31 week baby tolerate oral medication and is its absorption from gut reliable?
Reply to Reviewer 3: Thank you very much for your questions and suggestions. The title, methods and results of this study have been greatly modified. The youngest child included in the study was 34 weeks old, and this typo has been corrected. All subjects tolerated oral medication.

Reviewer 4:
Public Comments:
Ethics: This study is a clinical trial. Nothing was found about the registration and registration number of this study.
Title:
The title and running title need revising.
Reply to Reviewer 4: Thank you very much for your reminding. The ethical approval number of this study has been added to the method part, and the title and running title have been substantially revised.
Grammar correction is needed. The manuscript contains many grammatical errors.
Background:
"Line 47 and 48: GCV is a common broad-spectrum antiviral drug with high curative effects. It can treat symptoms due to CMV infection,"
Let be more specific. Replace the word "symptoms" with "manifestation" or a broader word to include signs and other CMV infection sequala.

Please correct the word "newonate" to "the neonate or newborn" in the whole document (>5 cases).
Provide reference in the following sentence.
Line 47-48 GCV is a common broad-spectrum antiviral drug with high curative effects.
Reply: Thank you very much for your reminding. The above grammatical errors have been corrected. The sentence of Line 47-48 has also been supplemented with a quotation for reference.
Methods:
Lines 99-100 (3) Comparison of hearing loss between the 2 groups during treatment by TEOAE hearing screening and BAEP
Please extend the acronym with first occurrence.
Line 81 Dose for the infusion was determined based on the body weight of 6mg/ml,
Correct 6mg/ml to 6 mg/kg?
Reply: Thank you very much for your comments. The first occurrence of the abbreviation has been supplemented with the full name. The typo on line 81 has been corrected.
Result:
Tables and result text should not be the repetition of each other.
Discussion
Generally accepted facts should not be mentioned as the result of this study. The discussion contains many basic science facts that are irrelevant to the principal argument of the study.
Lines 158-159: Hyperbilirubinemia is commonly known as jaundice clinically, Hyperbilirubinemia is not another term for jaundice. However, they refer to a similar condition. Clinically jaundice appears when bilirubin surpasses 2.5 mg/dl.

The limitation of the study should be addressed.

6. Conclusions
Conclusion: The conclusion should be deducted from the study's findings.
Reply: Thank you very much for your suggestions. The results and discussion sections

have been substantially revised to supplement some of the findings. The erroneous statement about jaundice has been corrected as requested. The limitations of this study have been given at the end of this paper. Some research results supporting this conclusion have been supplemented.

Associate Editor's Comments:

Associate Editor 1:

Public Comments:

Dear respected authors,

Thanks for considering the Iranian Journal of pediatrics for the submission of the paper. Let me inform you that the esteemed peer reviewers entirely appraised the article. The following characteristics have been denoted. Please highlight any change/response and added/deleted texts separately and with different colors. Please be aware that this appraise does not guarantee the eventual acceptance of the manuscript.

The decision about the manuscript is marginal, and the article needs complete rewriting. Carefully answer all issues regarding methods, improve the presentation of results and discussion. Please pay careful attention to the comments underneath this email to ensure that the editors and reviewers appraise the revised manuscript. This way, we can avoid future rounds of clarifications and revisions, moving swiftly to a decision.

When writing the review report, please take a moment to put yourself in the place of the authors and consider:

• If you received this report, would you find it constructive?

• Would you find the tone courteous and professional?

Reply: Thank you very much for your comments. The issues raised in the comments have been resolved and all of the comments have been replied.

Ethics: This study is a clinical trial. Nothing was found about the registration and registration number of this study. According to COPE for the studies conducted after 1995, registration is inevitable. According to IJP policy, and in accommodation with COPE ethic rules, registration of clinical trials in a formal registration system is inevitable. This code should be available at least before the study finalize. Please submit this code asap before the appraisal process long in the way. Otherwise, we cannot guarantee the publication of the article.

Reply: Thank you very much for your reminding. The Ethics Committee approval date and number have been added to the methods section.

Title:Both title and running title need compete revising."Effect of Valganciclovir and Ganciclovir on The Curative Effect and Hearing among Neonates with Congenital Cytomegalovirus Infection"The title should Identify the article/study as a randomized clinical trial.The following title might be relevant. "Comparative Effects of Valganciclovir and Ganciclovir on the Congenital Cytomegalovirus Infection and hearing loss, a randomized? Controlled? clinical trial"Running title:Valganciclovir Vs. Ganciclovir, Effects on Congenital CMVGrammar correction is strongly needed.

Reply: Thank you very much for your suggestions. The title and running title have been substantially revised.

Background:

Replace the word "symptoms" with "manifestation" or a broader word to include all

clinical presentations and CMV infection sequala.
Please correct the word "newonate" to "the neonate or newborn" in the whole document (5 cases).
Provide reference in the following sentence.
Line 47-48 GCV is a common broad-spectrum antiviral drug with high curative effects.

Reply: Thank you very much for your suggestions. The above grammatical errors have been corrected. The sentence of Line 47-48 has also been supplemented with a quotation for reference.

Methods:

What about randomization and controlled randomization?
Attentio should be paid to the standard follow-up of newborns afflicted by congenital CMV infection presenting with hearing loss according to high-quality references such as RedBook published by AAP.
188 Ethical Approval: The study was approved by the Institutional Ethics Committee of our Hospital.
Please send the approval Certificate to the IJP.
Lines 99-100 (3) Comparison of hearing loss between the 2 groups during treatment by TEOAE hearing screening and BAEP
Please extend all acronyms with the first occurrence.

Result:

Tables and result text should not be the repetition of each other.

Reply: Thank you very much for your suggestions. Randomization methods have been added to the methods section. The Ethics Committee approval date and number have been added to the methods section. The first occurrence of the abbreviation has been supplemented with the full name.

Discussion

For each part/paragraph of the result, there should be an equivalent counterpart in the discussion one by one that logically discusses that part. Each paragraph should discuss one topic of the result. Otherwise, that part/s should be deleted from the results. Jumping back and forth from one topic to another topic should be avoided. The manuscript contains 3 tables. However, their data are not discussed efficiently. A question arises as to why these results were added to the article if they are not to be discussed.
Lines 158-159: Hyperbilirubinemia is commonly known as jaundice clinically, Hyperbilirubinemia is not another term for jaundice. However, they refer to a similar condition. Clinically jaundice appears when bilirubin surpasses 2.5 mg/dl.
The classic definition of jaundice is a serum bilirubin level greater than 2.5 to 3 mg per dL (42.8 to 51.3 µper L) in conjunction with a clinical picture of yellow skin and sclera. One might have hyperbilirubinemia without clinical jaundice.
The limitation of the study should be discussed and added at the end of the manuscript.

6. Conclusions

Conclusion: The conclusion should be deducted from the study's findings. The author should avoid adding facts as the result of the current study.

Reply: Thank you very much for your comments. The erroneous statement about jaundice has been corrected as requested. The limitations of this study have been given at the end

of this paper. Some research results supporting this conclusion have been supplemented.

2 Revision 1

3 comments · 6 Nov 2021 – 14 Nov 2021

Referee 1 Reviewer — ACCEPT 6 Nov 2021

No comment

Elahe Norouzi Reviewer — ACCEPT 11 Nov 2021

The revised manuscript is accepted.

Ali Amanati Reviewer — REJECT 14 Nov 2021

Comments for authors
Thanks for submitting your revised manuscript. The authors' responses to my comments are unsatisfactory. I had hoped that the review would improve the manuscript to a level that could be accepted. Unfortunately, there are still significant deficiencies that cause the manuscript to fall short of that level. As evident in Table 2, after excluding the majority of included cases (21 cases) with normal hearing status, 12 cases in the control group and 15 cases in the observational group were compared. The comparison is more difficult with the addition of 9 infants with mild SNHL. So, the interpretation of the results is difficult, and in my opinion, the authors would not be able to achieve the study aim based on the results obtained. I am rejecting the manuscript.

3

Revision 2

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.

Dear editors,
Thanks for your advice to my manuscript, we are very pleased to be asked to submit a revision. The revisions have been made in accordance with the comments of the reviewers and the changes made within the text of the revised manuscript are indicated wih highlight. The following are our point-to-point responses to the editors' comments.
Thank you and best regards.
Your sincerely,
Zhaojun Pan

Reviewers' Comments:
Reviewer 1:
Comments for authors
Thanks for submitting your revised manuscript. Author responses are unsatisfactory for my comments.
I had hoped that the review would improve the manuscript to a level that could be accepted. Unfortunately, there are still significant deficiencies that cause the manuscript to fall short of that level. As evident in Table 2, excluding the majority of included cases (21 cases) who have normal hearing status, 12 cases in the control group and 15 cases in the observational group were compared. The comparison is more difficult with the addition of 9 infants with mild SNHL. So, the interpretation of the results difficult and in my opinion, the authors would not draw the study aim from obtained results and I am rejecting the manuscript.
Reply: Thank you very much for your valuable time and effort in reviewing this manuscript. Your comments and suggestions are so enlightening to us and are crucial to our future work. The purpose of this study was to elucidate the efficacy difference between valganciclovir and ganciclovir in the treatment of congenital cytomegalovirus infection, and then to illustrate the efficacy difference between the two in the treatment of hearing impairment. In addition, single-center studies resulted in a limited number of eligible neonates. For these reasons, not all of the included subjects had hearing impairment. The question you raised is indeed one of the limitations of this study. Thank you again for your valuable advice. In the future work, we will bear in mind the teachings and make more rigorous and perfect research.
Reviewer 2:
The revised manuscript is accepted.
Reply: Thank you very much for your valuable time and effort in reviewing this manuscript and your approval.
Reviewer 3:
No comment
Reply: Thank you very much for your valuable time and effort in reviewing this manuscript and your approval.
Associate Editor's Comments:
Associate Editor 1:
I have received the feedback from the reviewers and they are satisfied with the changes requested. I think it can be accepted.
Reply: Thank you very much for your valuable time and effort in reviewing this manuscript and your approval.
EIC Decision:

The authors have addressed the majority of our reviewers' concerns. Our reviewer has another comment which is below. Please consider these suggestions in revising your paper.

How to Revise?

Please sign in to the journal with your account and follow the instruction to resubmit your revised paper. To resubmit, we need to receive:

1) A word file including replies to all reviewers' comments (one-by-one)

Reply: Thank you very much for your valuable time and effort in reviewing this manuscript. We have completed a word file including replies to all reviewers' comments (one-by-one), as followings.

2) A highlighted manuscript word file (highlight all newly added sentences in your word file)

Reply: Thank you very much for your valuable time and effort in reviewing this manuscript. A highlighted manuscript word file (highlight all newly added sentences in your word file) has been completed, as attached.

Reviewer 1:

First, the Methods section. Treatment indication which used in this study is not fully matched with AAP guidelines and international consensus recommendations for congenital CMV management (newborns with normal hearing and mild SNHL have been included). However, if the authors determine the characteristics of newborns who already have SNHL despite treatment, the results of the study may be useful. This includes the determination of the primary severity group of newborns who have complicated with SNHL despite treatment. See, http://dx.doi.org/10.1016/S1473-3099(17)30143-3 and American Academy of Pediatrics. [Cytomegalovirus] In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[289].

Reply: Thank you very much for your pertinent and detailed comments and suggestions. The indications used in this study may not fully match some of the international consensus, but we have made some more local adjustments for the indications in order to enrich the comprehensive study data.

Second, the Methods section. The follow-up duration for monitoring SNHL (the main outcome) is short and is not in line with standard recommendations. See, the American Academy of Pediatrics Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, 4th Edition, which recommends hearing testing at 4, 6, 9, 12, 15, 18, 24, and 30 months of age. This should be considered as a study limitation.

Reply: Thank you very much for your pertinent and detailed comments and suggestions. The indications used in this study may not fully match some of the international consensus, but we have made some more local adjustments for the indications in order to enrich the comprehensive study data. Methods and dosages of VGCV and GCV have been added to the summary methods section. Some incorrect content has been removed.

Other shortcomings:

The title should be rewritten with better words.

Reply: Thank you very much for your suggestions. The title of this study has been revised with better words in text with highlight.

Lines 11-12: route of VGCV and GCV is not determined.

Reply: Thank you very much for your reminding. Methods and dosages of VGCV and

GCV have been added to the summary methods section.
Line 16: spell-out "BAEP"
Reply: Thank you very much for your reminding. Brainstem auditory evoked potentials (BAEP)
Line 46: remove "etc."
Reply: Thank you very much for your reminding. I have removed "etc."
Lines 47-52: drug forms is not determined. Determine oral versus intravenous formulation in the whole manuscript.
Reply: Thank you very much for your detailed comment. I have determined oral versus intravenous formulation in the whole manuscript.
Line 49: remove this part: "Oral administration of this drug has low utilization rate and 50 is also accompanied by side effects such as fever and chills.", oral formulation of GCV currently is not in use.
Reply: Thank you very much for your reminding. I have removed this part: "Oral administration of this drug has low utilization rate and 50 is also accompanied by side effects such as fever and chills."
Lines 51-52: remove this statement: "At present, for these 2 drugs, it is unclear which one is better for the symptoms of congenital CMV infection among newonates."; based on AAP recommendation both approaches (oral VGCV and intravenous GCV) are acceptable for the treatment of eligible CMV infected neonates. See, American Academy of Pediatrics. [Cytomegalovirus] In Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book: 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics: 2021[289].
Reply: Thank you very much for your reminding.I have removed this statement: "At present, for these 2 drugs, it is unclear which one is better for the symptoms of congenital CMV infection among newonates.".
Line 69-70: "symptoms" based on the 2015 5th International Congenital CMV Conference should be defined based on severity. A table should be provided for the determination of diagnostic criteria considered in this study and the proportion of newborns in the case and observational group meeting the diagnostic criteria from the 2015 5th International Congenital CMV Conference.
Reply: Thank you very much for your pertinent and detailed comments and suggestions. The indications used in this study may not fully match some of the international consensus, but we have made some more local adjustments for the indications in order to enrich the comprehensive study data.
Line 84: define how VGCV oral formulation is prepared for newborn infants.
Reply: Thank you very much for your detailed comment. Methods and dosages of VGCV and GCV have been added to the summary methods section in the revised text with highlight.
Lines 121-124. This statement is not informative and should be more descriptive based on hearing loss improvement in each group based on hearing loss severity. How many of those with severe and extremely severe SNHL improved and how much? How many of those with mild SNHL fully improved?
Reply: Thank you very much for your suggestion. Table 2 was significantly modified to more detail the improvement of hearing symptoms in both groups.
Line 274 (table-1): define "t-value" and "($\bar{x}\pm s$)"

Reply: Thank you very much for your pertinent and detailed comment. “t value” means test statistic, and "($\bar{x}\pm s$)" means mean plus or minus standard deviation.

Reviewer 2:

Although the subject of the study is not a novel work and the effectiveness of Valganciclovir is accepted in treatment of congenital CMV infection from one decade ago, the work of authors is appreciated if it is performed in their setting for the first time. The manuscript needs major revision, as it is mentioned subsequently:

- The title and running title should be edited; running title may be change from “Ganciclovir on the curative effect and hearing”!! to “curative effect of Valganciclovir in CMV infection”

Reply: Thank you very much for your correction. I have revised the running title to be “Effect of Ganciclovir on Cytomegalovirus Infection and its Effect on Hearing”.

- Abstract: background section is not sufficient and relevant. In first line of results, after “no statistical significant” the word “difference” should be added.

Reply: Thank you very much for your comment. The word “difference” has be added after “no statistical significant” in first line of results.

- Key words should be changed according to Mesh browser to: newborn, cytomegalovirus, Ganciclovir, Valganciclovir, infections

Reply: Thank you very much for your correction. Key words have been changed according to Mesh browser to: newborn, cytomegalovirus, Ganciclovir, Valganciclovir, infections.

- Background: what is the last word? “Newonates”?!!! please correct it wherever it is in the whole manuscript.

Reply: Thank you very much for your reminding. It’s should be “neonates”. I have corrected it wherever it is in the whole manuscript.

- Method: what is the method of the study? Clinical trial? Case-control? How many neonates are the population of the study which 48 out of them enrolled this study?

Reply: Thank you very much for your comment. The design method of this study has been added to the methodology section with highlight.

- Method: you mentioned that “no ROP” is one of your inclusion criteria, and all of your cases included in the study in first 15 days of life, so, how you assessed ROP before 28 days? Retinopathy of prematurity is an exclusion criteria not an inclusion one.

Reply: Thank you very much for your comment. The inclusion criteria were modified according to the actual situation.

- Method: how you evaluated “being allergic to therapeutic”? or do you mean anaphylaxis?

Reply: Thank you very much for your suggestion. The "allergy" referred to in this method refers to the condition in which the newborn is allergic to the Ganciclovir or Valganciclovir.

Reviewer 3:

Dear Author

please remove Title "objectives" in background.

Reply: Thank you very much for your reminding. I have removed Title "objectives" in background.

In Methods you should not write the results
Reply: Thank you very much for your reminding. I have removed the results from Methods.
Please check analysis method i think you have to write paired t-test and independent t-test.
Reply: Thank you very much for your suggestion, I have written paired t-test and independent t-test in the method.
In results just explain the parts that are not in the table.
Reply: Thank you very much for your comment. We have explained the parts that are not in the table with highlight.
can a 31 week baby tolerate oral medication and is its absorption from gut reliable?
Reply: Thank you very much for your question. The youngest child included in the study was 34 weeks old, and this typo has been corrected. All subjects tolerated oral medication.

Reviewer 4:
Public Comments:
Ethics: This study is a clinical trial. Nothing was found about the registration and registration number of this study.
Reply: Thank you very much for your reminding. The ethical approval number of this study has been added to the method part with highlight.
Title:
The title and running title need revising.
Reply: Thank you very much for your reminding. The title and running title have been substantially revised.
Grammar correction is needed. The manuscript contains many grammatical errors.
Reply: Thank you very much for your suggestion. The above grammatical errors have been corrected.
Background:
"Line 47 and 48: GCV is a common broad-spectrum antiviral drug with high curative effects. It can treat symptoms due to CMV infection,"Let be more specific. Replace the word "symptoms" with "manifestation" or a broader word to include signs and other CMV infection sequala.
Reply: Thank you very much for your reminding. We have replaced Replace the word "symptoms" with "manifestation".
Please correct the word "newonate" to "the neonate or newborn" in the whole document (>5 cases).
Provide reference in the following sentence.Line 47-48 GCV is a common broad-spectrum antiviral drug with high curative effects.
Reply: Thank you very much for your reminding. We have corrected the word "newonate" to " neonate" in the whole document. The sentence of Line 47-48 has also been supplemented with a quotation for reference.
Methods:
Lines 99-100 (3) Comparison of hearing loss between the 2 groups during treatment by TEOAE hearing screening and BAEP
Please extend the acronym with first occurrence.

Reply: Thank you very much for your comments. The first occurrence of the abbreviation has been supplemented with the full name.
Line 81 Dose for the infusion was determined based on the body weight of 6mg/ml, Correct 6mg/ml to 6 mg/kg?
Reply: Thank you very much for your comments. The typo on line 81 has been corrected.
Result:
Tables and result text should not be the repetition of each other.
Reply: Thank you very much for your suggestions. The results and discussion sections have been substantially revised to supplement some of the findings.
Discussion
Generally accepted facts should not be mentioned as the result of this study. The discussion contains many basic science facts that are irrelevant to the principal argument of the study.
Reply: Thank you very much for your reminding. Some research results supporting this conclusion have been supplemented.
Lines 158-159: Hyperbilirubinemia is commonly known as jaundice clinically, Hyperbilirubinemia is not another term for jaundice. However, they refer to a similar condition. Clinically jaundice appears when bilirubin surpasses 2.5 mg/dl.
Reply: Thank you very much for your suggestions. The erroneous statement about jaundice has been corrected as requested.
The limitation of the study should be addressed.
Reply: Thank you very much for your reminding.The limitations of this study have been given at the end of this paper.
6. Conclusions
Conclusion: The conclusion should be deducted from the study's findings.
Reply: Thank you very much for your reminding. The conclusion has been deducted from the study's findings.
Associate Editor's Comments:
Associate Editor 1:
Public Comments:
Dear respected authors,
Thanks for considering the Iranian Journal of pediatrics for the submission of the paper. Let me inform you that the esteemed peer reviewers entirely appraised the article. The following characteristics have been denoted. Please highlight any change/response and added/deleted texts separately and with different colors. Please be aware that this appraise does not guarantee the eventual acceptance of the manuscript.
The decision about the manuscript is marginal, and the article needs complete rewriting. Carefully answer all issues regarding methods, improve the presentation of results and discussion. Please pay careful attention to the comments underneath this email to ensure that the editors and reviewers appraise the revised manuscript. This way, we can avoid future rounds of clarifications and revisions, moving swiftly to a decision.
When writing the review report, please take a moment to put yourself in the place of the authors and consider:
• If you received this report, would you find it constructive?
• Would you find the tone courteous and professional?
Reply: Thank you very much for your valuable time and effort in reviewing this

manuscript. Your comments and suggestions are so enlightening to us and are crucial to our future work. The issues raised in the comments have been resolved and all of the comments have been replied.

Ethics: This study is a clinical trial. Nothing was found about the registration and registration number of this study. According to COPE for the studies conducted after 1995, registration is inevitable. According to IJP policy, and in accommodation with COPE ethic rules, registration of clinical trials in a formal registration system is inevitable. This code should be available at least before the study finalize. Please submit this code asap before the appraisal process long in the way. Otherwise, we cannot guarantee the publication of the article.
Reply: Thank you very much for your reminding. The Ethics Committee approval date and number have been added to the methods section.
Title:
Both title and running title need compete revising.
"Effect of Valganciclovir and Ganciclovir on The Curative Effect and Hearing among Neonates with Congenital Cytomegalovirus Infection"
The title should Identify the article/study as a randomized clinical trial.
The following title might be relevant.
"Comparative Effects of Valganciclovir and Ganciclovir on the Congenital Cytomegalovirus Infection and hearing loss, a randomized? Controlled? clinical trial"
Reply: Thank you very much for your suggestions. The title has been revised to be “Comparative Effects of Valganciclovir and Ganciclovir on the Congenital Cytomegalovirus Infection and hearing loss, a randomized controlled trial”.
Running title:Valganciclovir Vs. Ganciclovir, Effects on Congenital CMVGrammar correction is strongly needed.
Reply: Thank you very much for your suggestions. The running title have been substantially revised.

Background:
Replace the word "symptoms" with "manifestation" or a broader word to include all clinical presentations and CMV infection sequala.
Reply: Thank you very much for your suggestion. We have replaced the word "symptoms" with "manifestation" in the text with highlight.
Please correct the word "newonate" to "the neonate or newborn" in the whole document (5 cases).
Provide reference in the following sentence.
Reply: Thank you very much for your reminding. We have corrected the word "newonate" to " neonate" in the whole document.
Line 47-48 GCV is a common broad-spectrum antiviral drug with high curative effects.
Reply: Thank you very much for your suggestions. The sentence of Line 47-48 has also been supplemented with a quotation for reference.

Methods:
What about randomization and controlled randomization?
Reply: Thank you very much for your suggestions. Randomization methods have been added to the methods section.

Attentio should be paid to the standard follow-up of newborns afflicted by congenital CMV infection presenting with hearing loss according to high-quality references such as RedBook published by AAP.
Reply: Thank you very much for your pertinent and detailed comments and suggestions. The indications used in this study may not fully match some of the international consensus, but we have made some more local adjustments for the indications in order to enrich the comprehensive study data.
188 Ethical Approval: The study was approved by the Institutional Ethics Committee of our Hospital. Please send the approval Certificate to the IJP.
Reply: Thank you very much for your suggestions.The Ethics Committee approval date and number have been added to the methods section.
Lines 99-100 (3) Comparison of hearing loss between the 2 groups during treatment by TEOAE hearing screening and BAEP
Reply: Thank you very much for your suggestion. Table 2 was significantly modified to more detail the improvement of hearing symptoms in both groups.
Please extend all acronyms with the first occurrence.
Reply: Thank you very much for your suggestions. The first occurrence of the abbreviation has been supplemented with the full name.
Result:
Tables and result text should not be the repetition of each other.
Reply: Thank you very much for your suggestions. The results and discussion sections have been substantially revised to supplement some of the findings.

Discussion
For each part/paragraph of the result, there should be an equivalent counterpart in the discussion one by one that logically discusses that part. Each paragraph should discuss one topic of the result. Otherwise, that part/s should be deleted from the results. Jumping back and forth from one topic to another topic should be avoided. The manuscript contains 3 tables. However, their data are not discussed efficiently. A question arises as to why these results were added to the article if they are not to be discussed.
Reply: Thank you very much for your reminding. Some research results supporting this conclusion have been supplemented.
Lines 158-159: Hyperbilirubinemia is commonly known as jaundice clinically, Hyperbilirubinemia is not another term for jaundice. However, they refer to a similar condition. Clinically jaundice appears when bilirubin surpasses 2.5 mg/dl. The classic definition of jaundice is a serum bilirubin level greater than 2.5 to 3 mg per dL (42.8 to 51.3 µper L) in conjunction with a clinical picture of yellow skin and sclera. One might have hyperbilirubinemia without clinical jaundice.
Reply: Thank you very much for your suggestions. The erroneous statement about jaundice has been corrected as requested.
The limitation of the study should be discussed and added at the end of the manuscript.
Reply: Thank you very much for your reminding.The limitations of this study have been given at the end of this paper.

Conclusions
Conclusion: The conclusion should be deducted from the study's findings. The author should avoid adding facts as the result of the current study.

Reply: Thank you very much for your reminding. The conclusion has been deducted from the study's findings.

3 Revision 2

0 comments

No public comments in this round.