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OPEN PEER REVIEW

Comparison of Clindamycin with Other Anti-staphylococcal Antibiotics for the Treatment of Pediatric Staphylococcal Skin-Scaled Syndrome

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Contents

1 **Original submission** Referee 1, Associate Editor 2
2 **Revision 1** Referee 1 4
Authors' reply to reviewers 5
Reviewer and editor comments 10
3 **Revision 2** Associate Editor 11
Authors' reply to reviewers 12
Reviewer and editor comments 16

1 Original submission

2 comments · 13 Apr 2023 – 25 Apr 2023

Referee 1 Reviewer

MINOR REVISION 13 Apr 2023

Dear Editor-in-Chief of APID,
Regarding manuscript No. 136440, this cross-sectional study aimed to compare the effectiveness of clindamycin, alone or in combination with other anti-staph medications, in the management of pediatric 4S among patients admitted to a hospital in Iran from 2005 to 2021. The results showed significantly longer hospitalization in children who did not receive clindamycin. Comments for improvement of the manuscript are shown below:

Introduction:
Line 51: Please correct the spelling of "S. areous". Please correct the spelling of this bacterium throughout the manuscript (Table 2, "S. Aareus").

Results:
1. Lines 166-168: The following passage is repetitive: "The mean duration of hospital stay was 6.52 ± 1.90 days (minimum 3 and maximum 13 days). Also, the results showed that the average duration of recovery in these children was 4.90 ± 1.73 days (minimum 2 and maximum 11 days)."

2. If the data are available, please indicate the type of S. aureus infection in your cases according to susceptibility to oxacillin (MRSA and MSSA).

3. The names of antibiotics other than clindamycin are not presented in your results. Please indicate the names of other antibiotics that were prescribed with clindamycin. Please also correct lines 263-289 in the discussion section according to the antibiotics other than clindamycin that were prescribed.

Discussion:
Lines 243-253: Your data showed no significant difference in the duration of fever with clindamycin; however, a significant difference was shown in your study supporting the impact of this antibiotic on the elimination of fever in the 4S patients. It would be better to discuss this association first and then present your comparison with other studies regarding the duration of fever.
Lines 259-260: The sentence is not supported by your results as described above. In your results, the prevalence of fever was not higher in the group receiving clindamycin plus another antibiotic (Table 2).

Associate Editor

MINOR REVISION 25 Apr 2023

Dear Editor-in-Chief of APID,
Regarding manuscript No. 136440, this cross-sectional study aimed to compare the effectiveness of clindamycin alone or in combination with other anti-staph medications in the management of pediatric 4S among patients admitted to a hospital in Iran from 2005 to 2021. The results showed significantly longer hospitalization in children who did not receive clindamycin. Comments for improvement of the manuscript are shown below:

Reviewer 1:
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Results:
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3. The names of antibiotics other than clindamycin are not presented in your results. Please indicate the names of other antibiotics that were prescribed with clindamycin. Please also correct lines 263-289 in the discussion section according to the antibiotics other than clindamycin that were prescribed.

Discussion:
Lines 243-253: Your data showed no significant difference in the duration of fever with clindamycin; however, a significant difference was shown in your study supporting the impact of this antibiotic on the elimination of fever in patients with 4S. It would be better to discuss this association initially and then present your comparison of the duration of fever with other studies.
Lines 259-260: The sentence is not supported by your results as described above. In your results, the prevalence of fever was not higher in the group receiving clindamycin with another antibiotic (Table 2).

Reviewer 2:
line 5- "Staphylococcal scalded skin syndrome (4S) is a potentially life-threatening" / It is not potentially life-threatening.
line 37- The Introduction is too long, extending to line 118, and not all parts are related to 4S or the effect of clindamycin on Staphylococcus.
line 119- Materials and methods: Please explain why you categorized the cases into 3 groups. You wanted to show the effect of clindamycin, so it doesn't matter whether it was prescribed with or without other anti-staph drugs. You can divide patients into those treated with or without clindamycin.
"So that the length of time
line 186 - required for recovery and the length of hospitalization in the group without clindamycin was significantly longer (respectively, P = 0.018 and P = 0.002)." As mentioned above, if you choose 3 categories, you should compare the effect of dual therapy with clindamycin with that of clindamycin alone and treatment without it. The table only shows that therapy without clindamycin resulted in a longer hospital stay. What about dual therapy? Was that more effective than clindamycin alone?

line 193- Scaling is not a complication; it is part of the disease process, so please correct the table of complications.

line 245 - "Levison et al. compared the antipyretic effects clindamycin and penicillin and observed that clindamycin has better antipyretic effects on bacterial infection," ... Antibiotics don't have an antipyretic effect. When they control infection, fever diminishes, so it is not logical to refer to an antipyretic effect of penicillin, clida, or gentamycin on bacterial infection.

line290-294: In the results section of this study, the authors didn't mention the results of the comparison between combination therapy and the 2 other monotherapies, so how can you include this in the discussion?

The discussion needs revision.

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.

Reply to reviewers (clindamycin)

Dear reviewer 1:

Thanks for the constructive and complimentary comments on our article

1-According to your comment "*Staphylococcal scalded skin syndrome (4S) is a potentially life-threatening /it is not potentially life threatening*

The life-threatening term has been removed.

2-*line 37-introduction is too long , until 118 and all part are not related to 4s or effect of clindamycin on staphylococcus*

As much as possible, the introduction section is summarized.

3-*line 119-material and method:pls explain why did you categories cases to 3 part ,you wanted to show effect of clindamycin so it doesn't matter it prescribe with or without other antistasph drug ,you can divided patients whom treated with or without clindamycin*

Although our main goal was to compare the efficacy of clindamycin in 4S treatment, we aimed to investigate the effect of other antistaphs at the same time as a sub-target, because the effect of clindamycin alone may be different from clindamycin combined with another antibiotic. In other words, determine whether clindamycin administration is preferable, and if so, it should be administered alone or with an other antibiotic.

4-*line 186 - required for recovery and the length of hospitalization in the group without clindamycin was significantly longer (respectively, P = 0.018 and P = 0.002)..as mention above if you choose 3 category ,you should compare effect of dual therapy with clindamycin ,with clindamycin alone and without it ,,,,in table which present it just resulted therapy without clindamycin had longer stay in hospital ,what about daule therapy?it was more effective than clindamycin alone?*

As shown in Table 3, we compared 3 groups (receiving clindamycin, clindamycin with another antibiotic, and antibiotic regimen without clindamycin) in terms of duration of fever, duration of hospitalization and recovery time. As can be seen, the difference between the two clindamycin groups (with or without other antibiotics) was not obvious. Considering that the duration of length of time required for recovery and the length of hospitalization in the group without receiving clindamycin was longer than the other two groups, it will be in favor of the need to prescribe clindamycin. For further justification of the reason for dividing the patients into three groups, please refer to the explanation of item (3) in the upper section. I hope the explanations and corrections made will be acceptable to you.

5-line 193-scaling is not complication it is part of disease process ,so pls correct the table of complication

The item was corrected. We applied your valuable comment in text but no in the table(despite respecting your opinion). It is true that the most common finding in our patients was scaling, which can be a common finding of 4S course, but in some studies have shown that the use of clindamycin can induce skin shedding and even toxic epidermal necrosis in patient(as mentioned in discussion part). Therefore, it is challenging to compare this finding with antibiotic side effects. For this reason, in the table and statistical analysis, we classified and compared this finding among the complications.

6-line 245 -Levison et al. compared the antipyretic effects clindamycin and penicillin and observed that clindamycin has better antipyretic effects on bacterial infection,....antibiotics don't have antipyretic effect ,when they control infection fever diminished ,so it is not logical to say antipyretic effect of penicillin or clida or gentamycin on bacterial infection

Thanks to your comment. we have removed the term antipyretic effect of antibiotics and modified the sentence.

7-line290-294:in this study ,in result part ,authors didn't mention result of comparison between combination therapy and 2 other monotherapy ,so how you put it in discussion

What the authors mean is that the incidence of primary fever (before treatment) in the group receiving clindamycin beside another anti-staph agent, was higher than in the other two groups, rather than better fever control in this group. In other words, the recovery time and treatment duration were shorter in this group while they had a more common fever before initiating of antibiotic.

I hope the explanations and corrections made will be acceptable to you.

8- *discussion need revision .*

The discussion was reviewed and the necessary corrections were made.

Dear reviewer 2:

Thanks for the constructive and complimentary comments on our article

Line 51: Please correct spell of S. areous. Please correct spell of this bacterium throughout the manuscript (Table 2, S. Aareus).

We applied your comment and corrected spell of aureus. Thanks.

Lines 166-168: The sentence is repetitive (The mean duration of hospital stay was 6.52 ± 1.90 days (minimum 3 and maximum 13 days). Also, the results showed that the average duration of recovery in these children was 4.90 ± 1.73 days (minimum 2 and maximum 11 days).

With respect to the valuable comment, it is necessary to explain that the first item refers to the length of hospitalization and the second item is the time of beginning improvement of clinical symptoms (recovery time), which is not necessarily the time of discharge. These two item are not the same.

Please upon availability of data, indicate type of S. aureus infection regarding the susceptibility to oxacillin in your cases (MRSA and MSSA).

Thank you for your comment. Unfortunately, our study was retrospective and in our HIS data, we do not have available the type of S. aureus. If possible, it would definitely add to the value of the article.

Names of antibiotics other than clindamycin in your results are not presented. Please indicate names of other antibiotics which prescribed with clindamycin. Please also correct lines 263-289 in discussion section according to the prescribed antibiotics-other than clindamycin that were prescribed.

Necessary corrections were made and highlighted (Vancomycin and cloxacillin were the other agents used in the present study). The resistant rates of levofloxacin (8.33%), gentamycin (8.33%), tetracycline (25%), oxacillin (8.33%), vancomycin (0%) were significantly lower than the ones of erythromycin (100%), trimethoprim-sulfamethoxazole (TMP/SMX) (83.33%), clindamycin (91.67%), penicillin G(100%) in 4S patients in Yang et al study. They found that Vancomycin and oxacillin had the lowest resistance. But clindamycin resistance was common in Yang et al study and they did not recommend Clindamycin monotherapy for 4S.

Lines 243-253: While your data showed no significant difference for clindamycin in the reduction of duration of fever; however, a significant difference was shown in your study supporting the impact of this antibiotic for elimination of fever in the 4S patients. It seems better if this association be discussed initially, and then your comparison about duration of fever with other studies be presented. Lines 259-260: The sentence is not supported by your results as described above. In your results, the prevalence of fever was not higher in the clindamycin besides another antibiotic group (Table 2).

In this research, the evidence showed that the administration of clindamycin (alone or in combination) compared to other antibiotics does not show significant difference in reducing the duration of fever. What the authors mean is that the incidence of primary fever (before initiating of any therapeutic agent) in the group receiving clindamycin was higher than in the other two groups, rather than better fever control in this group. However, the recovery time and treatment duration were shorter in the clindamycin group who had a more common fever. I hope the explanations and corrections made will be acceptable to you.

Dear Associate Editor 1:

Thanks for the constructive and complimentary comments on our article

line 186 - required for recovery and the length of hospitalization in the group without clindamycin was significantly longer (respectively, P = 0.018 and P = 0.002). As mentioned above if you choose 3 categories, you should compare effect of dual therapy with clindamycin, with clindamycin alone and without it ,,,, in table which present it just resulted therapy without clindamycin had longer stay in hospital, what about daule therapy? Was that more effective than clindamycin alone?

The length of hospitalization and the duration of improvement of the initial symptoms were better in the group who had taken clindamycin.

Although our main goal was to compare the efficacy of clindamycin in 4S treatment, we aimed to investigate the effect of other antistaphs at the same time as a sub-target, because the effect of clindamycin alone may be different from clindamycin combined with another antibiotic. In other words, determine whether clindamycin administration is preferable, and if so, it should be administered alone or with another antibiotic.

As shown in Table 3, we compared 3 groups (receiving clindamycin, clindamycin with another antibiotic, and antibiotic regimen without clindamycin) in terms of duration of fever, duration of hospitalization and recovery time. As can be seen, the difference between the two clindamycin groups with or without other antibiotics was not obvious. Considering that the duration of length of time required for recovery and the length of hospitalization in the group without receiving clindamycin was longer than the other two groups, it will be in favor of the need to prescribe clindamycin. I hope the explanations and corrections made will be acceptable to you.

ine290-294: In this study, in results part, authors didn't mention result of comparison between combination therapy and 2 other monotherapy, so how you put it in discussion

This item was added according to your guidance in the discussion (the last paragraph of the discussion before the limitations of the study).

Comment 1: Lines 159-161 and lines 166-168 are similar, please delete one of these paragraphs.

We applied your comment and deleted one of the similar parts.

Comment 2: Sample size in each group is different, how did you assign the patients in each treatment group?

We appreciate your comment.
As you know, the main aim of this study was assessing all patients with 4s with a consensus method. Therefore, this comparison was indicated after sampling as a sub-scale analysis and provided different sample size in each group.

Comment 3: In table 2 and table 5, please report percent in addition to frequency in each cell.

We applied your comment.

Comment 4: In table 3, please report mean and SD in third row similar to first and second rows.

Thank you for your advice, it is corrected.

Comment 5: In table 5, which test did you use for comparing between three methods and different complications? some of cells in this contingency table are zero, did you note to this issue?

We applied Fischer's exact test and considered all zero numbers.

With regard

2 Revision 1

1 comment · 18 Jul 2023

Referee 1 Reviewer

MINOR REVISION 18 Jul 2023

Dear Editor-in-Chief of APID,
The authors responded to most of the comments and addressed them in the new revision. The following notes should be considered.

1. Please use the correct abbreviation of Staphylococcus aureus throughout the text after its first mention (i.e., "S. aureus").
2. Please add "value" after "p" to present the differences statistically (p value = 0.0018). p should be italicized too.
3. Please place a space between each number and the following parenthesis throughout the manuscript (e.g., n (%); 23 (43.3%), 17.6 (±10.68), etc.). Also, please replace N with n in the headings of the tables.

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.

Reply to reviewers:

Reviewer 1:

Thanks for the constructive and complimentary comments

1-introduction ; line 61-84 were deleted.

2- According to your comment : *line 216; most common finding in the treatment of 4S... what dose it mean ? finding in treatment !!!!*
the sentence was corrected:

The current research also showed that the most common complication seen during the course of the 4S disease was **scaling.**

3- According to your comment:

line 220 : Due to this problem, it seems that more diagnostic methods such as microbiological culture are needed to accurately differentiate them ,,,how microbiological culture can help us ???? 4s is toxin mediated disease ,how culture can help us that toxin is a complication or a finding of disease

You are right about the culture diagnostic method. The sentence was removed and it was modified like this. The difference between whether scaling is caused by the disease process itself or whether it is a therapeutic side effect cannot really be proven. Therefore, it is challenging to compare this finding with antibiotic side effects.

4—according to your comment :

line 248;In this regard, Kosior et al. found that clindamycin in adjuvant to other antibiotics reduces the

249 length of hospitalization in patients with various infections, including Staphylococcus aureus, which is consistent with the present study (43) what dose it mean? in various infection > which type of infection ?and what is the relationship of this sentence to your study?

Kosior et al. found that clindamycin in adjuvant to other antibiotics reduces the length of hospitalization in patients with various infections caused by Staphylococcus aureus, which is consistent with the present study.

the authors want to emphasize that the combination of clindamycin with other antibiotics in other infectious diseases caused by staph, in Koiser's study, had better results than the regimen without clindamycin.

5-*286- This issue can confirm the better effectiveness of clindamycin in combination with another anti-staph drug, at least in patients with worse general condition? finally you should advise to your reader that clindamycin cine alone or in combination has equal effect or which one is better ,because duale therapy has some significant side effect and your goal from chose 3 group is show the best model of therapy ,so add your clear result in this part.*

We again performed statistical analysis to compare the results between clindamycin alone and combined clindamycin groups for better conclusions

. The LSD post– hoc test was used to define the significant difference between each two groups. For better understanding, we defined three options for the post- hoc assessment as below:

Option 1: clindamycin alone versus clindamycin plus other antibiotics

Option 2: clindamycin plus other antibiotic versus without clindamycin

Option 3: clindamycin alone versus without clindamycin

The LSD post-hoc test showed that there was no significant difference . between groups in all options1, 2, and 3 (p=0.434, p= 0.4124, p= 0.976, .respectively)

Regarding the recovery time, results showed that despite no significant difference in option 1 (p=0.367), significant difference was noted for options 2 and 3 (p=0.017, p=0.006, respectively. In terms of hospitalization period no significant difference was obtained for option 2 (p=0.159). However significant difference was indicated for options 1 and 3(P=0.044, P=0.007, respectively). This result emphasized on the lower duration of hospitalization in patients who received clindamycin alone comparing to the group of clindamycin with another antibiotics (P=0.044).

Despite no difference in terms of duration of fever and recovery time, the present study showed that the patients who received clindamycin alone had

a shorter hospital stay than patients who treated by clindamycin plus another antibiotics.

Finally, among these three different therapeutic options, this study suggests clindamycin regimen alone for 4S patient. This study concluded that clindamycin (alone or in combination with other anti- staphylococcal agents) could shorten the recovery period of 4S and hospitalization in children. Besides it did not have any impact on the occurrence of complications. Also, the study concluded that the patients who received clindamycin alone had a shorter hospital stay than patients who treated by clindamycin plus another antibiotic. Considering the lower complications of mono therapy, lower cost, shorter length of stay ,we recommend clindamycin alone in treatment plan of 4S patients.

Reviewer 2:

Thanks for the constructive and complimentary comments

Please refer the correct abbreviation of Staphylococcus aureus throughout your text after its first presentation (i.e. "S. aureus"). Also please italicize the bacterial name in your text.

We advised your comment.

2-Please add "value" after "p" to present the differences statistically (p value= 0.0018). p should be italicize too.

Corrected.

3. Please place a space between number and parenthesis throughout the manuscript (exam: n (%); 23 (43.3%), 17.6 (±10.68)...etc . Also please replace N by n in the headings of the tables.

corrected

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3 Revision 2

1 comment · 26 Jul 2023

Associate Editor

ACCEPT 26 Jul 2023

Dear Editor-in-Chief of APID,
The manuscript was edited, and the authors responded to the comments in this revision. The manuscript is accepted; however, the correct spelling of S. aureus should be used in the manuscript at the proof stage.