OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

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

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Iranian Journal of Pediatrics
Article DOI: 10.5812/ijp.109797
Published in: Iranian Journal of Pediatrics: 31(2); e109797

Peer Review Report for "Aspirin Resistance in Children with Congenital Heart Disease and Its Relationship with Laboratory and Clinical Parameters"

Author(s): Sevcan Erdem, Eray Akay, Tolga Akbas, Fadli Demir, Nazan Ozbarlas

Review Timeline:

Submit Date: 4 Oct 2020
Revised Date: 4 Mar 2021
Accepted Date: 17 Mar 2021

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) — 28 Nov 2020

Dear AE,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: Associate Editor | **Revision** (0) — 1 Dec 2020

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (0) — 1 Dec 2020

Dear Author,

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

Answer to Reviewer 1

Major Issues

1- The result section provides too many in detail results with no discussion on them. The discussion section is written very disorganized with no good clinical judgment.

All results which are not statistically significant were excluded from the study. The discussion section has been rewritten. PT, PTT and INR values were not excluded from the study to show that the patients did not have any other coagulopathy.

2-There are too many results with no discussion on them. The result section is written rather vague. Too many results in detail with no discussion on them. Somewhere there is comparison between cyanotic heart disease with acyanotic ones, somewhere between aspirin resistance and aspirin responsive. What is the importance of comparison between cyanotic ones with acyanotics? Was this the aim of the study? As I understood only aspirin response between these groups may be important.

The aim of the study is 'aspirin responsiveness between the cyanotic and acyanotic patients'. Comparison between cyanotic heart disease with acyanotic ones excluded from the result and discussion sections.

3- Omit all results which are not statistically significant. What is the importance of mentioning them? OR if it is mentioned they should be discussed appropriately in the discussion section.

All results which are not statistically significant were excluded from the study. The results and discussion sections have been rewritten.

4-The discussion section is completely irrelevant to the results and is written rather vague. In many parts of the discussion section the results are repeated again.

All results which are not statistically significant were excluded from the study. The discussion section has been rewritten.

5-The discussion section should be re-written. At the current format it is not informative at all.

The discussion section has been rewritten.

6- Result is repeated again in the discussion section: there are many sentences like these in the discussion section:" this difference was not statistically significant (p: 0.414).”" In our study, there was a statistically borderline significance between oxygen saturation and aspirin resistance (p=0.055)."

These sentences were excluded from the discussion section and corrected.

7- What do authors mean by this sentence in the discussion section? Only a result has been provided with no discussion on that: "Although cyanotic patients were younger and had higher blood cell indexes in comparison to the acyanotic groups, there was no significant difference in age or blood cell indexes between aspirin responsive and resistant patients."

This sentence was about the patients in Helen's study. Corrected.

8- What did the author want to discuss with this section?: Although there are studies conducted in adults to determine whether higher doses can be more effective in patients with aspirin resistance

(18-20), all patients used similar doses of aspirin, and the relationship between the dosage and aspirin resistance was not evaluated."

This paragraph was excluded from the study as it was not aimed to find the effective dose.

9-Again, a new result is provided in the discussion section:" In our study, there was no statistically significant relationship between the groups using enteric coated and non-coated in terms of aspirin resistance (p=0.06)."

These sentences were removed from the discussion section and corrected.

10- Clarify this paragraph:" Drug interactions are important causes for aspirin resistance. A higher percentage of aspirin resistance in adults was observed among patients who take non-steroidal anti-inflammatory (NSAI) drugs (23), statin (24) and proton pump inhibitors (25). In our study, none of the patients were taking them. About a third of our patients (33.9%) used stomach protectors. All of them were taking H2 receptor blockers, instead of proton pump inhibitors as gastric protectors. Aspirin resistance was detected in 31.4% of these patients, this was not statistically significant."

The section on drugs not used by the patients was removed from the discussion. Only the results regarding the drugs used by the patients were discussed.

11-Provide a discussion for this result:" There was no statistically significant difference between the use of captopril and aspirin resistance in our study."

A discussion was added to provide for this result.

12-Too long and disorganized discussion regarding fibrinogen section.

The fibrinogen section was shortened and reorganized.

13- There is no discussion on this result:" In this study, it was determined that a history of thromboembolism in the patient are independent risk factors for aspirin resistance."

Discussion about the thromboembolism history of the patients was added.

Minor Issues

1- Provide a reference for the first paragraph of the objectives:" Aspirin is the most common used drug in the world and has been used to prevent thromboembolism in pediatric patients with CHD without conclusive evidence supporting its anti-platelet efficacy in these patients"

Provided references for the first paragraph

2- Clarify this sentence more:" However, there has been a poor correlation among the different tests to measure aspirin resistance and clinical aspirin resistance (5-7)."

A sentence was added for clarify this sentence more.

3- Re-write the study design with inclusion and exclusion criteria.

The study design with inclusion and exclusion criteria was rewritten.

4- This sentence should be in the result section not in the method section:" Their ages were between a month and 17 years (mean 56±51 months). "

This sentence was added to the result section from the method section.

5- The population should be in the result section, not in the methods:" Two populations of interest included (1) the patients with cyanotic CHD who underwent biventricular repair (n=24), single ventricle palliation, including those with Fontan procedure (n=4), bidirectional cavopulmonary anastomoses (n=6) and aortic to pulmonary arterial shunts (n=19); (2) the patients with acyanotic CHD following surgical repair of defects with synthetic patches (n=30), stent placement for coarctation of the aorta (n=2) or trans catheter device closure of atrial septal defect (n=18)."

The populations are in the result section now.

6- What do authors mean as described elsewhere?:" A routine laboratory analysis was performed including complete blood count; creatinine, urea, aspartate aminotransferase, alanine aminotransferase, and albumin levels in serum as described elsewhere"

This sentence was corrected.

7- Definition of aspirin resistance should be provided in the methods section.

Definition of aspirin resistance was provided in the methods section.

8- What do authors mean by this sentence?:does it mean aspirin responsiveness? The PAI defines the degree of ADP induced platelet aggregation in whole blood where values <4.7 PAI suggest that there is platelet dysfunction."

It means that there is aspirin responsiveness. This sentence was added to methods section; 'this means that there is an aspirin resistance when the PAI value ≥4.7'

9- Add "in pediatrics: in the following:" In literature, the incidence of aspirin resistance ranges from 2.3 to 80% through different laboratory studies IN PEDIATRICS".

'in pediatrics' was added.

10- We suggest rather than "we think" in the following section:" We think that the evaluation of platelet aggregation by peripheral blood smear will be a good guide in distinguishing clinical aspirin resistance from laboratory aspirin resistance.

'We suggest' was changed with "we think"

Answer to Reviewer 2

Background & Objectives

The patients with congenital heart disease (CHD), especially those undergoing cardiac surgery are at a higher risk for thromboembolism than other pediatric patients. -> please provide a reference and explain in detail!

References were added and explained in detail.

without conclusive evidence supporting its anti-platelet efficacy in these patients. -> please provide a reference and explain in detail!

References were added and explained in detail.

The term ‘aspirin resistance’ should be used in situations in which aspirin fails to hit its pharmacological target, documented with specific laboratory tests. The term ‘clinical resistance’ to aspirin should be used when aspirin is unable to prevent thromboembolic events. -> please name them "laboratory aspirin resistance" and "clinical aspirin resistance"!

Suggested changes have been made.

Results

Pulse oximetry saturation was lower in aspirin resistant patients but this difference was statistically significant at the border (p=0.055). -> If p<0.05 is significant, so 0.055 is not significant. However, you can write that it is very close to significance.

Suggested changes have been made.

No relationship was found between captopril (p=0.540), furosemide (p=0.835), stomach protection drugs (p=0.519), enteric coated aspirin use (p=0.060), and aspirin resistance. : stomach protection drugs-> gastric protective drugs. Also explain that use of enteric coated aspirin was very close to significance

Suggested changes have been made.

Discussion

but its effectiveness has not been tested in a clinical studies -> please provide a reference

References were added.

In our study, there was no statistically significant relationship between the groups using enteric coated and non-coated in terms of aspirin resistance (p=0.06). -> However it is very close and the small number of cases may be the major factor

Suggested changes have been made.

Drug interactions are important causes for aspirin resistance. A higher percentage of aspirin resistance in adults was observed among patients who take non-steroidal anti-inflammatory (NSAI) drugs (23), statin (24) and proton pump inhibitors (25). In our study, none of the patients were taking them. -> Please delete it

These sentences were deleted.

About a third of our patients (33.9%) used stomach protectors. All of them were taking H2 receptor blockers, instead of proton pump inhibitors as gastric protectors. Aspirin resistance was detected in 31.4% of these patients, this was not statistically significant. -> no clinical significance if there was not any positive relation in the literature

There are publications in the literature that H2 receptor blockers are preferred to protect against the effects of aspirin on the stomach.

OPEN PEER REVIEW

Revision (1)

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

REFEREE: Associate Editor | **Revision** (1) 9 Feb 2021

Dear EIC,
I thank the coauthors for revising their manuscript. Despite the negative opinion of our reviewer, the manuscript can be accepted if these improvements were done:
- First, a thorough English and scientific revision by an expert in writing scientific papers.
- Second, adding this sentence to Methods:
Considering the poor correlation between laboratory and clinical aspirin resistance, we did not change the antiplatelet regimen of our patients based only on the laboratory tests.
Thanks.

REFEREE: EIC | **Revision** (1) 11 Feb 2021

Dear Author
The second round of peer review of your manuscript is completed. I now have the reports of the Referee, which suggest that your manuscript needs more critical 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.

This improvements were done:

First, a thorough English revision was done by an expert in writing scientific papers. Certificate was added.

Second, this sentence was added to Methods:

Considering the poor correlation between laboratory and clinical aspirin resistance, we did not change the antiplatelet regimen of our patients based only on the laboratory tests.

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) 17 Mar 2021

Dear EIC,
Regarding the positive changes in the manuscript, it can be considered suitable for publication.
Thanks.

REFEREE: EIC | **Revision** (2) 17 Mar 2021

Dear Author,
The second round of peer review of your manuscript has been completed, and I am pleased to inform you that your manuscript has now been accepted for publication in our journal.
Thanks.