Author’s response to reviews

Title: Comparison of metamizole and paracetamol effects on colonic anastomosis and fibroblast activities in Wistar rats

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Version: 1 Date: 20 Dec 2019

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PHAT-D-19-00254

Comparison of metamizole and paracetamol effects on colonic anastomosis and fibroblast activities in Wistar rats

Eko Purnomo, MD, PhD; Dwi Aris Agung Nugrahaningsih, MD, MSc, PhD; Nunik Agustriani, MD; . Gunadi, MD, PhD

BMC Pharmacology and Toxicology

Dear Mr. Marcelo Arbo, Ph.D.

Our manuscript "Comparison of metamizole and paracetamol effects on colonic anastomosis and fibroblast activities in Wistar rats" (PHAT-D-19-00254) has been revised based on reviewer’s suggestions. We have responded all the questions and suggestions by overwriting the point by point. We really appreciate all those suggestions for this manuscript. We believe it would improve the manuscript and may allow a revised version to be published in BMC Pharmacology and Toxicology.
Reviewer reports:

(Reviewer 1): Vijayakumar Sekar, M.Sc.,PGDSP.,Ph.D

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

1. Comment : improve the background

Response :

We thank for the reviewer’s concern about the background. We have improved the background of our manuscript. All changes in the manuscript are indicated in the text by highlighting with yellow colour.

2. Comment : author provide the animal ethical committee number in the MS content

Response :

We thank to reviewer’s comment to the ethical approval number. This study has an approval from the Institutional Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito Hospital (KE/FK/1095/EC/2015). Our institutional Review Board has been accredited by Forum For Ethical Review Committees In The Asian and Western Pacific Region FERCAP. We have put the ethical committee number in the declaration of ethical aproval section (Ethical approval, page 10).

3. Comment : why author choose two different concentration in two different drugs??

Response :

We sincerely appreciate the reviewer’s question. We made an error about writing the paracetamol dosage as 50 mg/kg/day that it should be similar to metamizole dosage 60 mg/kg/day. We used the same dosage that have been used by Sanchez et al. from previous study. Therefore, we have revised our manuscript in the treatment of methods section (Treatment, line 4, page 4).
4. Comment: improve the language from native English speaker
Response:
We thank for the reviewer’s concern about the English language. To improve the English, a native English speaker has edited our manuscript. All revised in the manuscript are indicated in the text by using track changes.

5. Comment: avoid the typographical and grammatical errors
Response:
We really thank to reviewer’s comment about the typo and grammatical errors. We have corrected all typographical and grammatical errors. We have also consulted our manuscript to the native English speaker to improve our paper. All changes in the manuscript are indicated in the text by using track changes.

6. Comment: authors revise the all image text font style'
Response:
We have revised all image text font style based on reviewer’s suggestion.

7. Comment: add the histo image scale bar clearly, some images are not good quality
Response:
We sincerely appreciate to reviewer’s suggestion about the quality of image in figure 1. We have revised all image with the new better resolution images and put the clearer scale bar.

8. Comment: author add the fibroblast cell line images in the mail content
Response:
We have add fibroblast cell line images of migration assay from our study and put in the mail content.
9. Comment: author should be add the methods in following references

Response:

We really thank to the reviewer’s suggestion to add the methods in following references. We have put the references in the method section which have done based on previous study.

(Reviewer 2): Janet Mifsud de Gray, PhD

This is an interesting and well written paper which uses sound scientific evidence in support of its conclusions.

1. Comment: It is not clear however how the number of animals needed to make the study statistically valid estimated.

Response:

We appreciate reviewer’s comment to the number of animal in this study. We use 6 rats in each group of treatment to make the study statistically estimated. We have added this information in the methods section (Treatment, page 4).

2. Comment: In addition the paper would gain from supporting evidence showing how the results obtained from these animal studies can be transferred to the human situation.

Response:

We conducted this animal study based on the clinical data that showed a detrimental effect of NSAIDs on colon anastomosis. Thus, we used both NSAIDs, metamizole and paracetamol, that widely used as post-surgery analgesia in pediatric patients to compare their effects on rat colonic anastomosis. Based on our results study, we suggest that metamizole has the worst effect on colon anastomosis than paracetamol. Therefore, we prefer use paracetamol than metamizole as analgesic in the postoperative colon anastomosis.

We have added this information in the discussion section. (Discussion, in last paragraph page 9)
3. Comment: The raw individual data per animal supporting figures no 2 to 7 also need to be included in the paper, with the relevant statistical analysis to support the figures as drawn.

Response:

We have provided raw individual data per animal supporting figures no.2 to 7 as an excell document in the mail content.

4. Comment: In addition, in lines with established norms, more information needs to be provided on the 3Rs taken in the care of these animals and measures taken to reduce suffering.

Response:

We really thanks for reviewer’s suggestion about 3Rs aspect in our study. All animals in our study were maintain in international standard animal facility in the best possible conditions and got the best possible care from skilled and experienced animal caregiver. Thus, we conducted our in vivo study based on The ARRIVE guidelines checklist. We have added those information in the method section.

(Subjects, Line 3-5, page 3)