Author’s response to reviews

Title: A study on combination of daptomycin with selected antimicrobial agents: In vitro synergistic effect of MIC value of 1 mg/L against MRSA strains

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Author’s response to reviews:

Dear Academic Editor and Reviewers:

We thank all the reviewers for all the valuable and constructive comments to improve our manuscript entitled "In vitro activities of daptomycin in combination with other antimicrobial agents against MRSA strains with a daptomycin MIC value of 1 mg/L determined by checkerboard analysis". We have revised the manuscript according to your suggestions. Please see our point-by-point replies below.

Review Comments to the Author

Md Zakirul Islam, MBBS, MPhil (Reviewer 1): Please fix the formatting errors, increase the quality of language, represent the data or results by relevant graphs or charts.

Ans.: Thank you for your comment. We have made the corresponding amendments based on your suggestions (Page 5, Lines 75, 76-77, 81-82, 83-84 of the “Manuscript”; Page 6, Lines 95, 102, 103-105 of the “Manuscript”; Page 13, Lines 205-208 of the “Manuscript”; Page 17, Lines 290-295, 296 of the “Manuscript”; Page 18, Lines 301-304, 308 of the “Manuscript”). Our manuscript has been sent for English editing and rewrote accordingly. The proof was appended in the end. Figure 1 was added in the manuscript to represent the data or results (Page 30, Figure 1).
Santosh Kumar, PhD (Reviewer 2): The study is a good piece of work, but there are many loopholes.

1. Firstly the title needs to be modified, it is quite lengthy.

Ans.: Thank you for your precious comment. We have modified the title as below which was suggested by another reviewer:

A study on combination of daptomycin with selected antimicrobial agents: In vitro synergistic effect of MIC values of 1 mg/L against MRSA strains (Page 1, Lines 1-4).

2 There is no proper justification to why the combination of fosfomycin, gentamicin, linezolid, oxacillin and rifampicin were tried.

Ans.: Thank you for your comment. According to one review (Steenbergen et al. JAC 2009), the synergistic interactions were found in selective incidences with daptomycin and oxacillin, daptomycin and rifampicin, daptomycin and gentamicin. In Reference 14, the combination of daptomycin with fosfomycin was interpreted as 100% of synergistic effect. In Reference 26, a combination of daptomycin plus linezolid was more effective than one agent alone against MRSA strains in biofilms. However, these previous reports did not focus on MRSA isolates with a high daptomycin MIC. To sum up, this is why the combination therapies with daptomycin and fosfomycin, gentamicin, linezolid, oxacillin, or rifampicin against MRSA strains with high MIC for daptomycin were tried.

3. The authors claim to have studied 100 MRSA strain and for each drug 4 dilutions above and below the MIC and probably the data set might have been done in triplicates. This means 8 concentrations for 100 strains means 800x3=2400 for one drug. Likewise the data is for 6 drugs means 2400x6=14400 test, which is a huge data, but doesn't seem this huge data from the tables. Further have they taken the average of the 100 strains, that is also not specified. The SD values are also missing.

Ans.: Thank you for your precious comment. We indeed performed lots of laboratory tests for measuring of MIC, and for each drug, every MRSA isolate would be tested for its MIC for at least two times. If the difference between the two runs of testing was within one dilution, the higher one would be interpreted as its actual MIC. The testing might be triplicated if the difference was beyond one dilution in the first two runs of testing. To determine the geometric means and standard deviations of the MIC values and then used them to perform combination testing were impractical because it needed extremely intensive labor in formulating the concentrations of tested drugs without justified benefits to do so. The MICs to the tested drugs of every individual isolates were listed in the supplement file.
4. The concentration of daptomycin has been specified as 1mg/L, but the concentration of other drugs are not mentioned either in the text or in the table 2 where the combination has been tried.

Ans.: Thank you for your comment. Please see the supplementary file also, which showed the MIC of other drugs. If the actual MIC value was higher than the tested upper limits (128mg/L of fosfomycin, 256mg/L of gentamicin, 256mg/L of oxacillin, 64mg/L of rifampicin), since such high levels of drug concentrations could not achieve in clinical situation and therefore it was not practical to determine the actual MIC, we treated the MIC levels as the tested upper limits in the combination tests.

Nik Ahmad Shaiffudin Nik Him, MD, MMed (Emerg. Medicine) (Reviewer 3):

It was a pleasure to review this interesting article

Title   A complete and lengthy title

In vitro activities of daptomycin in combination with other antimicrobial agents against MRSA strains with a daptomycin MIC value of 1 mg/L determined by checkerboard Analysis

May be shortened as below:

A study on combination of daptomycin with selected antimicrobial agents: In vitro synergistic effect of MIC value of 1 mg/L against MRSA strains

Ans.: Thank you for your precious comment. We have shortened our title as your advice (Page 1, Lines 1-4).

Abstract

The background should highlight on the current knowledge of clinical updates of the treatment using daptomycin in combination with fosfomycin and why this study is conducted.

Ans.: Thank you for your comment. We have highlighted clinical updates of the treatment using daptomycin in combination with fosfomycin and the reason why this study is conducted in the section of Background within the Abstract (Page 3, Lines 44-48).
Background

To add content or references with regards to following

1. Definition of MRSA nosocomial infection
2. Current treatment guidelines for MRSA for both locally and internationally

Ans.: Thank you for your precious comment. We have added the content of “definition of MRSA nosocomial infection” and “current treatment guidelines for MRSA” in the text (Page 5, Lines 77-79, 85-90).

Materials and method

Fair / Additional statistic application/ description is preferred

Ans.: Thank you for your comment. We have added additional statistic description in the text (Page 9, Lines 158-159; Page 10, Line 179).

Table and images

Fair

Ans.: Thank you for your comment.

Result

Promising findings

Ans.: Thank you for your comment.

Discussion

To add the additional or added value from the result that may change the current practice.

Ans.: Thank you for your precious comment. We have emphasized the combination therapy of daptomycin with fosfomycin on the influence of clinical practice (Page 14, Lines 235-238).
Conclusions

This combination (daptomycin and fosfomycin) is already known to be an effective treatment as compared to monotherapy.

Ans.: Thank you for your precious comment. We have modified the above sentence (Page 18, Line 311).

Reference

To follow journal guides for author

Ans.: Thank you for your comment. We have followed journal guides for author.

Others

English & grammar have to be proof read thoroughly to make the article more comprehensible.

This study is publishable. Thank you

Ans.: Thank you for your comment. Our manuscript has been sent for English editing and rewrote accordingly. The proof was appended in the end.

We appreciate those comments and suggestions to improve the quality of our manuscript. Thank you again for your kind attention to our manuscript and consideration for publishing our manuscript in “BMC Pharmacology and Toxicology”.

Sincerely yours

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