Author’s response to reviews

Title: High dose statin prophylaxis in cardiopulmonary bypass related surgery: clinical utility. A randomised controlled trial.

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Version: 1 Date: 15 Mar 2017

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Version: 3 Date: 15 March 2017

Author’s response to reviews: see over
The Biomed Central Editorial Team


Thank you for consideration of our manuscript for publication in your journal.

We have reviewed the above manuscript according to your reviewer’s comments.

Reviewer #1:

1. Type of statin given to the control group. Note that the molecular structures of statins are not similar and could have an effect on the mechanism of action.

Please refer to page 5, paragraph 1, line 5. Patients are either on Atorvastatin or Simvastatin as these are the two most commonly used statin therapy in our practice and both are similar in the molecular structure. We excluded those on Rosuvasatin due to the differences in potency of Rosuvasatin as compared to Atorvastatin and Simvastatin.

2. The timepoint of the second measurement of the Troponin I level is missing (Results page 10).

We only chose 2 timepoints for the measurement of Troponin I, one at baseline and one at 4 hours post removal of cross clamp. Previous study (unpublished) from our team showed that Troponin I level at 5 minutes post removal of cross clamp was not statistically significant, hence we opted not to include that in this study.

3. Spelling errors: "significant differences were testing", "As practicing clinician, we advocate"

Please refer to page 8 paragraph 2 line 9. Spelling error “significant difference were testing” is amended to ‘significant differences were testing’

Please refer to page 14 paragraph 3, line 7. Spelling error “As practicing clinician, we advocate” is amended to “As practicing clinicians, we advocate”
Reviewer #2:

1. This paper was well written and design. But I think the number of patients is not sufficient for this study. The power analyses should be required in this study statistically. There are many factors that affect the response to systemic inflammation. More parameters should be assessed with a wider patient population.

Please refer to page 5 paragraph 1 line 13. We performed a power analysis after the initial 10 patients were recruited. This demonstrated a total number of 30 patients (15 in each arm) were needed to adequately power the IL-8 and MMP-9 analysis. A clinical end-point was not chosen, as it would involve a large number of patients, which would require multicentre perhaps international cooperation. Our purpose is to lay the groundwork for such a study.

We appreciate the reviewer’s advice for the assessment of more parameters and will undertake such measure for our subsequent studies.

2. Preoperatively two weeks are very long time in patients undergoing CABG. In which patient do you think to give statin therapy preoperatively? After your study did you start to give high dose statin therapy in your patients routinely.

Please refer to page 5 paragraph 2 line 6. The duration of 2 weeks at which patients in the investigation arm received atorvastatin 80mg is based upon our previous study, which demonstrated that neutrophil migration is attenuated following 2 weeks exposure of high-dose statin.

We intend to give the high dose statin therapy preoperatively in all patients who are scheduled for elective surgery 2 weeks or more from the time of listing.

Please refer to page 14 paragraph 3 line 8. Some of our consultants have indeed started to give high dose statin therapy to their patients scheduled to undergo CABG, while a few others have yet to commit to this practice.

3. What are the hepatic effects of statins in patients undergoing CABG with cardiopulmonary bypass? Did you evaluate to hepatic functions in study patients. And What do you think about this subject?

Please refer to page 9 paragraph 1 line 3 and page 27 Table 2. Liver function test at time of randomisation and after 2 weeks of treatment were similar in both groups, with no hepatic side effects documented in patients (Table 2).
Reviewer #3:

Title:

- The title should be more representative of the content (i.e., high dose statins) since your control group is being treated with oral statins as well.

Please refer to page 1 line 1. Title is amended to “High dose statin prophylaxis in cardiopulmonary bypass related surgery: clinical utility. A randomised controlled trial.”

- Is "on-pump cardiac surgery" more accurate than "CPB related surgery"?

The authors would prefer to keep the title as “cardiopulmonary related surgery”, instead of “on-pump cardiac surgery” as the study is focused on the systemic inflammatory response secondary to the use of cardiopulmonary bypass.

Abstract:

- Conclusion> optimising the dose of the pre-operative statins is a vague expression; in your study you tested the effect of increasing the dose only.

Please refer to page 2 line 20. “optimising the dose of pre-operative statins” is replaced with “high dose preoperative statin therapy”.

Clinical trial register: it sounds like a long duration from 11/2012 till now considering studying 30 patients only ... do you have an explanation for this?

There are only 30 patients recruited during the period of November 2011 to June 2014. The difficulty lies on the recruitment of patients and planning for their elective surgeries. If a patient who is recruited into the study and is randomised to the investigation arm, the statin therapy will be altered to Atorvastatin 80mg for a minimum of 2 weeks. Ideally the elective surgery will be performed as planned, however, many patients cannot wait for 2 weeks for their surgery. Moreover, if an emergency operation has to be carried out on a sicker patient, priority has to be directed towards the emergency operation. This will have an impact in the study group, thus making recruitment of more patients a challenge.
Methods:

- The control group included those who were on statins (<40) you should specify the type of statins?

Please refer to page 5, paragraph 1, line 5. Patients are either on Atorvastatin or Simvastatin as these are the two most commonly used statin therapy in our practice and both are similar in the molecular structure. We excluded those on Rosuvastatin due to the differences in potency of Rosuvastatin as compared to Atorvastatin and Simvastatin.

- Ignoring the duration of statin therapy (Confounding variable) may affect the reliability of your results?

Please refer to page 5 paragraph 2 line 6. The duration of 2 weeks at which patients in the investigation arm received atorvastatin 80mg is based upon our previous study, which demonstrated that neutrophil migration is attenuated following 2 weeks exposure of high-dose statin.

Results:

- Any explanation for the higher neutrophil count in the investigation arm over the first 2 days post-operatively inspire of the lower SIRS markers level?

Please refer to page 12 paragraph 4 line 3. “we observed a trend of higher neutrophil count in the investigation arm over the first 2 days post-operatively in spite of the lower IL-8 level. We proposed that this is probably due to the result of statin in attenuating neutrophil migration, resulting in higher level of extracellular neutrophil”

Discussion:

- Please summarise the discussion.

The authors felt that the discussion section is adequate as the statement detailed the reason for carrying out this research, which included all the previous work from our team which led to this randomised controlled trial.

- Explain how your findings can affect our clinical practice!
Please refer to page 14 paragraph 3 line 5. This study has laid the groundwork for future studies looking into recruiting more patients with multicentre cooperation. As practicing clinicians, we advocate the use of high-dose preoperative statin therapy in patients undergoing CPB related surgery.

Consent for Publication:

Please revised your Consent for publication with the following.

“Written informed consent was obtained from the patient('s legal guardian or next of kin) for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.”

Please refer to page 18 paragraph 1 line 4. Revision done and consent for publication is replaced as “Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.”