Author's response to reviews

Title: A Randomised Controlled Trial of Ivabradine and Atorvastatin in Emergent Orthopaedic Lower Limb Surgery: A Mechanistic Study of Peri-Operative Myocardial Injury and its Prevention Using Computed Tomography Coronary Plaque Imaging and Novel Biomarkers of Cardiovascular Stress and Lipid Metabolism: study protocol for a randomized controlled trial.

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Author's response to reviews: see over
July 2, 14

Editor in Chief,
BMC Trials Journal.


Dear Editor,

Thank you for the opportunity to address the reviewer’s feedback and provide a revised version of this manuscript. In the revised document we have improved on the abstract and discussion part, revised the primary and secondary outcomes, and have incorporated other suggestions made by the reviewers. Furthermore, we have also provided the details about the ethics approval number (HREC P06/12) and the current trial status, which is actively recruiting.

A point-by-point response follows. Please do not hesitate to be in touch should you require any further clarification.

Yours Sincerely

Dr M Asrar ul Haq
Editorial Comments:

1. Please ensure the title conforms to journal style for study protocol articles. The title should follow the format ?_________: study protocol for a randomized controlled trial.?

The title has been amended accordingly.

2. Please include the reference number given with ethical approval with your ethics statement in the Methods section.

The references number has been added to the methods section.

3. Please include a trial status section. This should state the status of the trial at the time of manuscript submission. The journal considers study protocol articles for proposed or ongoing trials provided they have not completed patient recruitment at the time of submission.

A “Trial Status” section has been added before the primary outcomes section.

Reviewer’s Comments

1. When it comes to the primary outcomes tested in this study (perioperative MI incidence and magnitude after randomization to Rx therapy), the type of study (RCT) and statistical analyses used are appropriate. However, correlations between cardiac biomarkers, platelet activity markers, plaque burden and perioperative MI would have been better looked into with separate observational studies, which would have required the application of different protocols and statistical methods. There are many assumptions of causality that need to be made to confirm or invalidate the complex mechanistic hypotheses formulated by the investigators. As a result, I don't think that the study
design – or at least how it is reported – adequately test them and will lead to significant conclusions.

Thank you for the comment and supporting the design for primary outcome. We agree with your viewpoint regarding the secondary outcomes. Accordingly, we have removed some of the secondary outcomes and prioritized the others. We believe that these secondary outcomes although may not lead to any definitive conclusion like you mentioned, would however be additional events of interest and might be helpful in explaining the primary effect.

The updated outcomes are:

Primary outcome measure
Based on the peak Troponin I level post surgery day 1, 2, 3 and 4, the frequency (binary outcome) and magnitude (continuous variable) of new myocardial injury following emergent orthopaedic surgery for lower limb fracture. Troponin I > 0.04 µg/L is considered positive in our reference laboratory.

Secondary outcome measures
1) Myocardial infarction according to the universal definition
2) NT-proBNP (pmol/L), MR-proANP (pmol/L), MR-proADM (nmol/L) and CT-proET-1 (pmol/L) (Markers of myocardial stress)
3) sPLA2 and Lp-PLA2 mass and activity (Markers of plaque burden described in percent)
4) Death in-hospital, at 30 days and 12 months
5) Stroke in-hospital, at 30 days and 12 months

Safety Outcomes
1) Symptomatic bradycardia or heart block requiring cessation of Ivabradine
2) Liver enzyme elevation > 3 times the upper limits of normal (ALP, GGT, AST and ALT measured in U/L)

2. Outcomes: Unclear definitions of primary outcomes. Many secondary outcomes for which patients will be screened for during follow-up don’t
appear in the list. Where is the LFTs outcome coming from? I would have liked measurement units to be given for each outcome. How is plaque burden evaluated and reported (there’s a clear protocol on the acquisition technique but not on how it will be used)?

The definition of primary outcome has been revised as per below:
“Based on the peak Troponin I level post surgery day 1, 2, 3 and 4, the frequency (binary outcome) and magnitude (continuous variable) of new myocardial injury following emergent orthopaedic surgery for lower limb fracture. Troponin I > 0.04 µg/L is considered positive in our reference laboratory.”

Furthermore:
1) We have revised the secondary outcome section as per above.
2) We have further clarified the ambiguity in some outcome measures including LFT (as per statin safety protocol).
3) Units have been added to all measures.
4) We have improved the protocol section of evaluation of plaque burden and have added the following table:

<table>
<thead>
<tr>
<th>Calcium Score (2, 3)</th>
<th>Implication</th>
<th>Risk of Coronary Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No identifiable plaque</td>
<td>Very low, generally less than 5 percent</td>
</tr>
<tr>
<td>1 - 10</td>
<td>Minimal identifiable plaque</td>
<td>Very unlikely, less than 10 percent</td>
</tr>
<tr>
<td>11 - 100</td>
<td>Definite, at least mild</td>
<td>Mild or minimal coronary</td>
</tr>
<tr>
<td></td>
<td>atherosclerotic plaque</td>
<td>narrowings likely</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>101 - 400</td>
<td>Definite, at least moderate atherosclerotic plaque</td>
<td>Mild coronary artery disease highly likely, significant narrowings possible</td>
</tr>
<tr>
<td>401 or Higher</td>
<td>Extensive atherosclerotic plaque</td>
<td>High likelihood of at least one significant coronary narrowing</td>
</tr>
</tbody>
</table>

**Minor Essential Revisions**

1. **Randomization:** OK description. What about blinding? Please Clarify

Thank you. The patients will undergo an open label process in randomization as described in methods:

“Prospective, single centre (Northern Hospital), open label, randomized 2x2 factorial controlled trial of Ivabradine and Atorvastatin in the prevention of myocardial injury following emergent orthopaedic surgery for lower limb fracture.”

2. **Sample size calculations:** Would have been better reported in words... e.g. “we estimated that ___ patients would be required to have a power of ___% (alpha = ___, two-tail) to identify a difference PMI incidence of ___.”

Thank you for your valuable suggestion. It has been amended accordingly:

“We estimated that 200 patients would be required to have a power of 0.94 (alpha = 0.05, two tail) to indentify a moderate sized effect (0.25) in PMI incidence between the groups”
3. The writing quality is fair but there are many typo and spelling mistakes, inconsistencies in capitalization, incomplete sentences and inappropriate use of verb tenses. The overall quality of the abstract section is poor and doesn’t summarize well the full article.

Thank you. We have revised the abstract and performed through spelling and grammar check.

4. The background section, despite being quite interesting, appears too long as compared to the methods section and lacks a clear structure as compared to other study protocols published on Trials.

Thank you for the comment, we have revised the background session and summerised it further.

5. Discussion: I would have appreciated a word on feasibility and expected impact as opposed to a summary of the background section and hypotheses.

We have revised the discussion session and highlighted the main expected impacts.