Author's response to reviews

Title: Meta-Analysis of Randomized Controlled Trials on Magnesium in Addition to Beta-Blocker for Prevention of Postoperative Atrial Arrhythmias after Coronary Artery Bypass Grafting

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Author's response to reviews: see over
Dear Editors:

Thank you for your review and editorial suggestions on our manuscript, entitled: Meta-Analysis of Randomized Controlled Trials on Magnesium in Addition to Beta-Blocker for Prevention of Postoperative Atrial Arrhythmias after Coronary Artery Bypass Grafting (MS: 4694024808235558). We have worked on them based on all your suggestions point-by-point. The use of English has been carefully modified based on the advices of two native English speakers. The revised version of our manuscript has been submitted. This cover letter gives a point-by-point response to the concerns.

Referee 1(Reviewer: Fausto Biancari):

1. Introduction: the first and second sentences repeat the same concept: the authors could delete the first one.

Response to the review: we have deleted the first sentence in the 'Introduction' section.

2. Postop. stroke is the major complication related with postop. atrial fibrillation (Lahtinen, Ann Thorac Surg). This should be added to the Introduction section.

Response to the review: we have added the information to the first paragraph in the 'Introduction' section (AF, occurring after CABG, is also a major determinant of postoperative stroke [3].) and added a reference (3. Lahtinen J, Biancari F, Salmela E, Mosorin M, Satta J, Rainio P, Rimpiläinen J, Lepojärvi M, Juvonen T: Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 2004, 77: 1241-1244.).

3. Corticosteroids have been evaluated to reduce the risk of postoperative AA. Please add this information to the Introduction section.

Response to the review: we have added this information to the first paragraph in the 'Introduction' section (Although moderate-dosage corticosteroid should be considered for the prevention of AF in high-risk patients undergoing cardiac surgery, the interaction between corticosteroids, beta-blockers, and amiodarone requires further

4. The authors should report details regarding their criteria for defining heterogeneity.

Response to the review: we have reported details regarding the criteria for defining heterogeneity in the 'Statistical methods' section. (We assessed heterogeneity with $I^2$, which describes the percentage of total variation across studies due to heterogeneity rather than chance. $I^2$ can be calculated as: $I^2 = 100\% \times (Q - df)/Q$ (Q = Cochrane’s heterogeneity statistics, df = degrees of freedom). Negative values of $I^2$ equaled zero, so that $I^2$ ranged between 0% (ie, no observed heterogeneity) and 100%. High values would show increased heterogeneity [17]. Data were considered to be heterogeneous if the chi-square generated by RevMan heterogeneity test was associated with a $P$ value <0.05.) and added a reference (17. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 2002, 21:1539-1558.).

5. “For the outcome of interest (occurrence of AA after CABG), odds ratio (OR) with 95% CI was used.” The authors should report also this endpoint as risk ratio.

Response to the review: we have reported occurrence of AA after CABG as risk ratio in the 'The pooled treatment effect' section. (The pooled OR and risk ratio (RR) of all studies, by the fixed effects model, did not show that combination of magnesium and beta-blocker significantly decreased the incidence of postoperative AA after CABG verse beta-blocker alone (OR 1.12, 95% CI 0.86-1.47, $P = 0.4$; RR 1.09, 95% CI 0.89-1.34, $P = 0.4$) and little heterogeneity was indicated ($P = 0.41$, $I^2 = 0\%$ and $P = 0.44$, $I^2 = 0\%$, respectively).).

6. “The combination of magnesium and beta-blocker group was higher than beta-blocker alone group in the risk of postoperative adverse events”: please rephrase this sentence.

Response to the review: we have rephrased this sentence in the 'The pooled treatment effect' section. (The risk of postoperative adverse events was higher in the combination of magnesium and beta-blocker group than beta-blocker alone group).
7. “Limitation of our study include limitations inherent in any retrospective analysis”: this is not a retrospective study!

Response to the review: we have deleted this sentence in the 'Limitations' section.

**Referee 2(Reviewer: Richard Cook):**

1. The grammar needs to be reviewed and corrected.

Response to the review: the use of English has been carefully modified based on the advices of two native English speakers.

2. The conclusion that Mg is associated with greater adverse events is not defended well enough by the manuscript to be justified. There is not enough discussion of what those adverse events were, and what the theoretical basis is for those adverse events. Since only 3 studies were used to come to this conclusion, it is perhaps too strong a statement to conclude that Mg in addition to beta blockers induces more adverse events. It would be more appropriate to say that there you observed an association with more adverse events in those pts who received Mg.

Response to the review: we have discussed those adverse events of Mg in the 'Limitations' section *(Each included trial had different categories of adverse events. For example, the trial by Bert et al [19] demonstrated postoperative adverse events that included myocardial infarction and ventricular ectopic activity, whereas the trial by Geertman et al [21] only included serious bradycardias and nonsustained ventricular tachycardia. The research by Solomon et al [23] showed the adverse events including bradycardia and hypotension.) and the potential theoretical basis for those adverse events in the fourth paragraph in the 'Discussion' section (The majority of adverse events were bradycardia and hypotension. An explanation for this phenomenon could be that intravenous administration of magnesium prolongs sinoatrial node conduction time, atrioventricular nodal refractory period, and PR and atrial-His intervals, as shown in electrophysiologic studies in healthy human subjects [37]. It is assumed that these effects are amplified when magnesium is combined with beta-blocker. Further specific studies are needed to evaluate this hypothesis.)*; we
have added a reference (37. Kulick DL, Hong R, Ryzen E, Rude RK, Rubin JN, Elkayam U, Rahimtoola SH, Bhandari AK: Electrophysiologic effects of intravenous magnesium in patients with normal conduction systems and no clinical evidence of significant cardiac disease. Am Heart J 1988, 115:367-373.); we have corrected some sentences to say that we observed an association with more adverse events in those pts who received Mg in the 'Conclusions' (Moreover, we observed an association with more adverse events in those people who received magnesium and beta-blocker.).

**Editorial Requests:**

1. Title page: please include a title page at the front of your manuscript file. It should contain, at minimum, the names, institutions, countries and email addresses of all authors, and the full postal address of the submitting author.

   **Response to the review:** we have added a title page at the front of our manuscript file.

2. Competing interests: manuscripts should include a 'Competing interests' section. This should be placed after the Conclusions/Abbreviations.

   **Response to the review:** we have added a 'Competing interests' section placed after the Conclusions.

3. Authors' contributions: Please include an 'Authors' contributions' section before the Acknowledgements and Reference list.

   **Response to the review:** we have added an 'Authors' contributions' section before the Acknowledgements and Reference list.

4. Acknowledgements: We strongly encourage you to include an 'Acknowledgements' section between the Authors' contributions section and Reference list.

   **Response to the review:** we have added an 'Acknowledgements' section between the Authors' contributions section and Reference list.

5. We recommend that you ask a native English speaking colleague to help you copyedit the paper.
Response to the review: the use of English has been carefully modified based on the advices of two native English speakers.

If there are any problems, please order me to solve them.

Thank you very much for your attention and consideration.

Sincerely,
Congxia Wang

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December 19, 2012