Author's response to reviews

Title: Efficacy and safety of ondansetron in preventing postanesthesia shivering: a meta-analysis of randomized controlled trials

Authors:

Hong-Tao Tie (hongtaotie@163.com)
Guang-Zhu Su (suguangzhu@163.com)
Hao-Wei Yuan (yuanhw568@163.com)
Jun-Huan Mou (junhuanmou@126.com)
Kun He (kun_he@126.com)
Shao-Rong Liang (shaorong_liang@126.com)

Version: 2
Date: 24 January 2014

Author's response to reviews: see over
Dear Prof. Marielette Costoy, Martin Esken and Parvin Sajedi:

I appreciate your instructive comments and suggestions to improve the previous manuscript (ID: 1682543311019849). We have addressed your suggestions and revised our manuscript. We also determine to resubmit it to *BMC Anesthesiology* for publication because this version (R1) has improved largely.

In addition, we have changed author lists since they provided lots of helps in the process of this work and payment can be paid by the new corresponding author.

So I expect this paper can be published in the *BMC Anesthesiology*.

Thank you very much!

Sincerely yours,
Reviewer: Martin Esken

Minor Essential Revisions:
1. There are several grammatical errors, which should be corrected before publication.

Response: A native English-speaking American has edited the entire manuscript. We believe this has significantly improved the language issues. Revisions in our manuscript were marked by red.

Discretionary Revisions:
2. Could you comment on ondansetron's side effects (for example headache) and compare the benefit of reducing PAS, and the benefit of reducing PONV, to the incidence of headache or other side effects? (If the data exits in the papers reviewed)

Response: We agree entirely with your insightful suggestions. All the ondansetron's side effects have been analyzed in our meta-analysis on the condition that proper data exist in included studies. Additionally, we have added other complications in our manuscript, as follows:

Apart from the primary outcome of PAS and side effect of bradycardia, other side effects were also mentioned but were not appropriate for quantitative analysis, among which none indicated a significant risk of convulsion, myoclonus, rush, pruritus, headache, pain, hypotension, sedation, nausea or vomiting.

3. Can you recommend changes to current practice in anesthesia? Ondansertron is given almost routinely in my institution for PONV prophylaxis, so I'm not sure how this will change my practice.

Response: Maybe. A novel clinical practice being recommended to current practice should be based on plenty of credible clinical evidences. Clinical evidence undoubtedly needs lots of clinical trials and other ways (e.g.: meta-analysis, case-report). We hold the idea that our meta-analysis contributes much more, than single clinical trial, to the clinical evidence, though it could not suffice to recommend changes to current practice in anesthesia. When enough, convinced clinical evidence
exists, the change may occur.

**Reviewer: Parvin Sajedi**

Reviewer's report:

1. **What is beginning time of your study in methods section?**

   **Response:** The first step, designing the protocol, was on the beginning of June 2013. The first step of execution, the literature search, was carried out on July 2013 as described in our manuscript. We think you might concern whether our manuscript was outdated with increasing original studies published. With the same search strategy (ondansetron AND shivering), the number of potential studies retrieved from PubMed was 17, just as the same as we did on 16 Jan 2014 (figure 1).

2. **Is it safety only not happening bradycardia? What about other complications?**

   **Response:** We agree entirely with your insightful suggestions that the complications should be analyzed as much as possible. However, a meta-analysis is based on the original data of studies reviewed. All the ondansetron's complications have been analyzed in our meta-analysis on the condition that proper data exist in included studies. Additionally, we have added other complications in our manuscript, as follows:

   *Apart from the primary outcome of PAS and side effect of bradycardia, other side effects were also mentioned but were not appropriate for quantitative analysis, among which none indicated a significant risk of convulsion, myoclonus, rush, pruritus, headache, pain, hypotension, sedation, nausea or vomiting.*

3. **With attention to differences between shivering in GA and neuraxial anesthesia, is it suitable to enter both studies in this meta-analysis?**

   **Response:** Yes. According to the “PICOS” principle of meta-analysis, the “I” in our meta-analysis is anesthesia involving general anesthesia and neuraxial anesthesia. The issue you concerned may be the heterogeneity for involving both general anesthesia and neuraxial anesthesia. In our meta-analysis, the heterogeneity ($I^2$) varies between
0% and 66.0%. Exploring the source of heterogeneity by sensitive analysis and forest plots, we found the study by Browning et al, which found ondansetron does not reduce the incidence of shivering, contributed to the heterogeneity identified. The subgroup analysis also confirmed the source of the heterogeneity is from the study instead of anesthetic technique. Moreover, we also discussed the mechanism why they differ, as follows in manuscript:

**Shivering differs from general anesthesia to neuraxial anesthesia.** General anesthesia could impair the central thermoregulation, while neuraxial anesthesia impairs both central and peripheral thermoregulation, by enlarging interthreshold range via raising the sweating threshold and decreasing the vasoconstriction and shivering thresholds. The core temperature decrease will be in a plateau after 3-4h in general anesthesia but no plateau appears in the neuraxial anesthesia, because the vasoconstriction will be evoked when the core temperature triggers the reset vasoconstriction threshold in general anesthesia but not neuraxial anesthesia. Thus, more heat will be lost, and more incidences will occur in neuraxial anesthesia. However, in our analysis, there was no difference in the risks of PAS between general and neuraxial anesthesia. It might be explained by short duration of the operation, and limited sample sizes, different heat preservation measures after operation.