Author's response to reviews

Title: A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron on postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron

Authors:

Jung-Hee Ryu (jinaryu@lycos.co.kr)
Ji-Eun Lee (lively12@gmail.com)
Young Jin Lim (limyjin@snu.ac.kr)
Hee-Pyoung Park (hppark@snu.ac.kr)
Deok Man Hong (limyjin@snu.ac.kr)
Hee Jung Baik (baikhi@ewha.ac.kr)
Kyeong Tae Min (ktmin501@yuhs.ac)
Hyunzu Kim (aneshyunzu@yuhs.ac)
Jong In Han (ryujh@snubh.org)
Sang-Hwan Do (shdo@snu.ac.kr)

Version: 2
Date: 21 May 2014

Author's response to reviews: see over
**Editorial requirements:**

1. Please list the full names, institutional addresses and email addresses for all authors.
   
   : Full names, institutional addresses and email addresses for all authors are listed in the title page.

2. Kindly include the Trial Registration Number and date of registration after abstract.

   : Trial Registration Number and date of registration was included in the last line of the abstract


3. Change `disclosure' to `competing interests'.

   : `Disclosure' was reworded with `competing interests'

4. Authors' contributions

   : Authors’ contribution was added as follows.

   “JHR, YJL, HJP, KTM and SHD contributed study design. JEL, DMH, HPP, JIH, and HZK collected and analyzed data. JHR and SHD drafted the manuscript. JHR, HJB and KTM made critical revisions of the manuscript. All authors read and approved the final analysis of the manuscript.”

5. Acknowledgements

   : Acknowledgements was added in the manuscript.

   “The authors thank MRCC (medical research cooperation center) of Seoul National University Bundang Hospital for their statistical assistance.”

6. Please include CONSORT checklist as additional file.

   : CONSORT checklist was added as additional file

7. Requesting copyediting:
After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

: The manuscript was revised by the English editing company and this was re-submitted the company again according to the comment.

Reviewer's report

Title: A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron on postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron

Version: 1
Date: 13 April 2014
Reviewer: Mohamed Abdulatif

Reviewer's report:

A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron on postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron

A randomized double-blind multicenter study evaluating the prophylactic anti-emetic potentials of ramosetron with two dose levels of ondansetron in adult patients undergoing elective craniotomy. The study hypothesis is original and important. However, I have the following structured comments:

Abstract:

1. The discrepancy between the number of patients in the methods and results sections is confusing. It is better to present in the abstract the number of patients who completed the study and were included in the final statistical analysis.

: We agree with your comment and the following sentence was included in the result of abstract.

"Among 161 patients, 127 patients completed the study and were included in the final analysis.” (Page 2, 14-15th line)

2. The first sentence in the results section in the abstract is too long and is difficult to understand.

: The sentence was reworded with the following one.

“The incidence of PONV were lower (nausea, 14% vs. 59 and 41%, respectively; P < 0.001;
vomiting, $P = 0.048$) and the incidence of complete response was higher (83% vs. 37 and 59%, respectively; $P < 0.001$) in group C than in groups A and B 48 h postoperatively.”

(Page 2, 15-17th line)

**Methods:**

3. There is discrepancy between the ASA physical status in the abstract and in the methodology (I-III versus I-II).

: We apologize for the discrepancy in the ASA physical status. We first tried to enroll the ASA physical status I-III patients but the analyzed patients were ASA physical status I or II patients. The ASA physical status in the abstract was corrected with I-II (Page 2, 6th line).

4. 1) An intracranial pressure > 15 mm Hg was considered as an exclusion criterion. Please explain how you managed to measure precisely the intracranial pressure in all patients preoperatively.

2) A Glasgow coma scale < 9 was considered as an exclusion criterion. Would a patient with a Glasgow coma scale of 9 be able to communicate effectively?

: Thank you for bringing this point of confusion to our attention. These exclusion criteria were selected to include patients who could freely communicate after surgery. Actually, all patients were scheduled to undergo elective neurosurgery and don’t need to measure invasive intracranial pressure preoperatively as they didn’t show symptoms of increased intracranial pressure. In addition, patients with Glasgow coma scale of 9 would not be able to communicate effectively as you pointed out. Most patients finally analyzed have Glasgow coma scale of 15. We apologize that this was not clear in the manuscript and those exclusion criteria were deleted from the method (Page 6, 14-15th line).

5. “Temperature was monitored using an esophageal stethoscope maintained at 36 ± 1°C throughout surgery”. How come an esophageal stethoscope was used to monitor and maintain core temperature?!!

: This is our mistakes and the sentence was reworded with as follows. “Temperature was monitored using an esophageal stethoscope and maintained at 36 ± 1°C with a warm pad throughout surgery.” (Page 7, 9-10th line)
6. Were patient kept NPO (nothing per os) postoperatively for the 48 hours study period?

: NPO policy may differ from institutes. Patients usually began sips of clear water after postoperative 4 hours and started the meal the day after the surgery.

7. Why an alpha error of 0.0175 was chosen for sample size calculation?

: We requested the statistics of this study to the MRCC (medical research cooperation center) of our hospital. They say that there are 3 groups in this study and Bonferroni correction was done by using 0.05/(number of groups = 3) for Type 1 (alpha) error. Therefore, 0.0175 was used for alpha error.

8. The minimum calculated sample size of 46 patients in each group was not finally achieved in any of the three study groups (Figure 1, CONSORT diagram).

: Thank you for pointing this out. Reduction by 30% in PONV was considered clinically significant and 46 patients per group were calculated. We chose 55 patients per group assuming a 20% drop-out rate. Total patients needed were distributed among 4 centers. However, we feel sorry that more patients than we expected have been dropped out during the study period and 46 patients in each group was not finally achieved.

9. Please specify the Post-hoc test used to find out which group is statistically different.

: Post hoc comparisons were made with Bonferroni’s correction. Bonferroni’s correction was done by using 0.05/(number of group) for Type 1 (alpha) error. This was added in the result (Page 9, 5th line). Each table suggested inter-group difference using † (<0.0175 compared with Group A) and ‡ (< 0.0175 compared with Group B).

Results:

10. The incidence of nausea and vomiting in different groups at different assessment time points is grossly duplicated in text and in table formats. It is desirable to point out to the main overall findings or trends in the text part of the results and refer to the appropriate table/s for the numerical values.
According to the comment, result was simplified with description on the main overall findings or trends (Page 10, 2nd and 3rd paragraphs).

11. The authors did not comment on the possible difference between the two dose levels of ondansetron.

The authors appreciate this comment. Statistically significant differences in the incidence of PONV or complete response were not observed between A and B groups throughout the study period. This was added in the result section (Page 10, 15-17th line).

Discussion:

12. There is considerable duplication of results section.

The authors agree with the comment and the following duplicated sentences were deleted from the discussion.

“In the current study, ramosetron 0.3 mg was superior to ondansetron 4 mg or ondansetron 8 mg for the prophylaxis of PONV in adults after craniotomy.” (Page 12, 1st paragraph)

“and the results of the present study showed that administration of 0.3-mg ramosetron at the time of dural closure was more effective than ondansetron 4 or 8 mg for the prevention of PONV.” (Page 12, 3rd paragraph)

“In the current investigation, there were no differences in the incidence of other adverse events such as drowsiness and dizziness among the three groups.” (Page 13, 2nd paragraph)

13. It is desirable to explain why ramosetron is more effective than ondansetron.

These phenomena could be explained by the potency of the two drugs. Results of previous meta-analyses showed that ramosetron was effective for preventing PONV without adverse effects and also had statistically significant differences for prevention of early and late PONV compared with ondansetron (Page 13, 14-17th line).

14. It is important to specify in the final conclusion statement that patients were managed by total intravenous anesthesia using propofol and remifentanil.

The authors appreciate this suggestion and the final conclusion was reworded as follows.
“Intravenous administration of ramosetron 0.3 mg at the end of surgery was more effective than ondansetron 4 or 8 mg for the prevention of PONV in patients undergoing elective craniotomy under total intravenous anesthesia using propofol and remifentanil. Future studies of multimodal prophylactic strategies with ramosetron and other antiemetics in this high-risk patient population are needed.” (Page 15, 2-4th line)

References:

15. This section needs careful revision to match the standard reference format adopted by most of the biomedical journals.

: Thank you this comment and the references were revised according to the standard reference format.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

Reviewer's report
Title: A prospective, randomized, double-blind, and multicenter trial of prophylactic effects of ramosetron on postoperative nausea and vomiting (PONV) after craniotomy: comparison with ondansetron
Version: 1 Date: 22 April 2014
Reviewer: Omar Adel Omar

Reviewer's report:
- Major Compulsory Revisions
  None
- Minor Essential Revisions
  None
- Discretionary Revisions
  1- (Grammar) Second paragraph of introduction “After craniotomy, PONV occurs with incidences up to 30–60% for emesis, and 15–70% for nausea when no prophylactic antiemetic is administered.”, and other locations where the authors
mention incidences “up to” then present a range of % instead of the maximum incidence, I recommend either mentioning a range from “x” to “y” or if using “up to” would only present the maximum incidence.

According to your comment, those sentences are changed to following words.

“Postoperative nausea and vomiting (PONV) is one of the most common perioperative concerns, with a relatively high incidence of up to 73% after craniotomy” (4 Page, 1-2nd line) “After craniotomy, PONV occurs with incidences up to 60% for emesis, and 70% for nausea when no prophylactic antiemetic is administered (Page 4, 7-9th line)”

2- In the second paragraph of the discussion, the authors mention the previous studies by Pugh et al and Fabling et al where ondansetron had been compared to metoclopramide and droperidol respectively in neurosurgery and showed the superiority of the latter agents, would it have been more informative for absolute efficacy of the agent of interest in the study to have been compared to such agents instead of ondansetron.

This idea is worth mentioning in the discussion unless the authors wanted to address 5-HT3 receptor antagonists in particular or for this stage of the studies to be followed or propose the follow up study comparing ramosetron to metoclopramide and, or droperidol.

The authors appreciated the comment. We concluded that think the content was not suitable for the result of the current study and deleted the following sentences (Page 12, 2nd paragraph).

“Pugh et al.[5] compared ondansetron with metoclopramide and found that metoclopramide 10 mg was more effective than ondansetron 8 mg for the prophylaxis of PONV in neurosurgical patients. Fabling et al.[1] reported that both ondansetron 4 mg and droperidol 0.625 mg were effective for the prevention of nausea, but only droperidol was effective in reducing vomiting episodes for patients with supratentorial craniotomy.”

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.