Author's response to reviews

Title: The Choice of Airway Affects The Incidence of Postoperative Nausea and Vomiting in Post-Anesthesia Care Unit Following Knee Surgery

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

The authors of this article would like to thank the reviewers and editor for their important suggestions regarding the PONV manuscript. Extensive revision were made and authors hope it will satisfy journal requirement for publications.

Response to reviewer one:

Major compulsory revisions:
1. Define primary and secondary goals of the study. Primary goal was to find whether choose of airway devices during anesthesia influence on PONV. Secondary goal was to find if there is significant difference in the incidence of PONV in ETT subgroups with or without nitrous oxide (N2O) and LMA subgroups with or without N2O as well as to explore predictors for PONV in patients undergoing knee surgery.

   The aims of the study was revised

2. There are a lot of confounding factors in this study and predictive risk scor for PONV should be used. I suppose that predictive model for PONV was used for antiemetic prophylaxis and authors might have that data.

   Sinclair score was used.

3. Postoperative pain and pain management (use of opioides) could influence on the incidence of PONV. Collected data about opioides and non opioid medications that were given to patients should be noted.

   Data about opioides and non opioides presented

Minor Essential revisions:
1. Abstract

   Background. First and second sentence of the abstract are general, don’t give us new informations and can be deleted. Before last sentence (aim of the study…) it would be necessary to clarify what is contradictory in previously published studies about influence of different airway devices (AD), laryngeal mask airway or endotracheal tube (LMA or ETT) during anesthesia with or without emetogenic anesthetic nitrous oxide (N2O) on the incidence of PONV.

   Correction made

   Methods. In the first sentence „patients who had knee surgeries …“ we suggest to add here „under general anesthesia“ and clarify please, that anesthesia
technique and antiemetic prophylaxis were not standardized as well as rescue treatment. ...

Correction made

Line 8: "...PONV as the primary outcome. Let us know here that PONV was followed just in PACU (hours?). Finally, measurement of postoperative pain could be of crucial value since pain and opioid analgesia could contribute to PONV. On the other way bias might occur. Add here data about postoperative pain and pain treatment!
PACU follow up to 8 hours and post operative pain was discussed,

Conclusion. The question is: why PONV incidence was higher in ETT group? Maybe because of longer duration of anesthesia in ETT group and other factors which could contribute to bias of examination (for example, different concentration of nitrous oxide, reversion of neuromuscular blockade in ETT group, nonstandardized antiemetic regimen, retrospective nature of the study,) ...so, it could be added that a prospective, randomized, placebo controlled study could give better answer.

Correction made.

2. Introduction must be rewritten.
Authors recited risk factors for PONV such as female gender, non-smoker, h/o MS and PONV, surgery time, volatile anesthetics, nitrous oxide and neostigmine > 3.0 mg based on results from Nitahara's et al. study (Nitahara K et al. Eur J Anaesthesiol 2007; 24: 166-70). Actually, only female gender was predictor for PONV during 48 hrs after vitrectomy and female gender, lower BMI and type of anesthesia were predictors for early nausea in that study. So, it would be better to add another reference here!

Reference added.

Authors postulated that middle ear pressure (MEP) and postoperative nausea and vomiting may be influenced by the choice of airway device (AD) during anesthesia (laryngeal mask airway, LMA vs endotracheal tube, ETT) but did not mention possible mechanism, for example obstruction of the otopharyngeal tube and stimulation of different parts of the airway.

obstruction of the otopharyngeal tube added

Authors cited previous findings of Nader's study group (Nader ND et al. Laryngoscope 2004;114:883-6) suggesting that higher barometric changes in MEP gradient in the nitrous oxide treatment group was associated with higher
frequencies of PONV. Moreover, authors cited preliminary findings that N2O may increase PONV in a dose-dependent fashion but which concentrations of N2O were used in this retrospective study were not noted.

N2O concentration was limited to 50% added

The use of LMA increased MEP gradient more than ETT when nitrous oxide was used for anesthesia maintenance but the difference in the incidence of PONV did not reach statistical significance in Nader's study. Contrary, another study (Hohlrieder M et al. Anesth Analg 2006; 102:319-21) showed higher MEP in nitrous oxide group but MEP was not influenced by the choice of AD during anesthesia with or without nitrous oxide. The same author (Hohlrieder M et al. Br J Anaesth 2007; 99:576-80) found that LMA reduced the absolute risk of PONV by 40% in comparison to ETT in females undergoing general anesthesia without nitrous oxide. This reference (Hohlrieder M et al. Br J Anaesth 2007; 99:576-80) could be added to others in the introduction section to emphasize dilemma about choice of AD and nitrous oxide during inhalational anesthesia which may contribute to the MEP gradient and increase incidence of PONV.

This reference (Hohlrieder M et al. Br J Anaesth 2007; 99:576-80 was added.

Other authors (Swann DG et al. Anaesthesia 1993; 48: 431-434) found a higher incidence of PONV in LMA group than in ETT group following inhalational anesthesia with nitrous oxide. It would be appropriate to list recently published studies about this problem in one table with number of patients in compared groups, airway device applied, type of surgery, anesthesia techniques, duration of surgery/anesthesia, main outcomes (primary and secondary) and statistical significance.

A table was created

Line 22 Define primary and secondary aim of this study. (Primary goal was to find if there is significant difference in the incidence of PONV between ETT and LMA groups. Secondary aim was to find if there is significant difference in the incidence of PONV in ETT subgroups with or without N2O and LMA subgroups with vs without N2O as well as to explore predictors for PONV in examined population ( no PONV vs PONV groups). .....)

Correction made

3.Methods
Page 4.
Line 9 „ neostigmine doses in excess of 0.05 mg /kg…” How many patients in
both groups (ETT group and LMA group) received neostigmine in doses #2.5 mg? There is doubt that doses of neostigmine 2.5 mg or higher might contribute to higher incidence of PONV. (References with contradictory results about neuromuscular reversal are as follows: Tramèr MR, Fuchs-Buder T. Br J Anaesth 1999; 82: 379-86. and Cheng C-R, Sessler DI, Apfel CC. Anesth Analg 2005; 101: 1349-55.) The question is about 2.5 mg of neostigmine rather than 3.0 mg.

We have included the number of patient in table

Line 10. Add here demographic data such as history of motion sickness (MS) and PONV or smoking status etc. (important risk factors for PONV)
Line 11. „nitros oxide „, in which concentrations was it used in your patients........ „volatile anesthetics“ add here (isoflurane, sevoflurane etc...) „neuromuscular blocking drugs...“ what kind of NMB drugs were used (vecuronium, rocuronium...). Additionaly, was perioperative fluid replacement in your institution liberal or restricted? Perioperative fluid replacement may play a role in the occurrence of PONV.

All corrections made

Line 12 „....neuromuscular reversal agents ...“ list here NM reversal agents and coadministered drugs. There are patients who did not receive NMB and reversal agents so, add here yes/no as outcome variables. Did you find more neostigmine coadministration with atropine or glycopyrrolate? It is overall known that coadministration of atropin has antiemetic effect reducing incidence of nausea whereas glycopyrrolate does not.

All patients were reversed with neostigmine/glycopyrolate

Line 13. „The incidence of PONV as assessed „..... „The incidence of PONV was assessed...“ „

correction made.

Line 14 „ The use of antiemetic ...“ The use of rescue antiemetic ...“ What kind of medications were used and in what average doses for antiemetic prophylaxis as well as rescue treatment? Let us know if rescue medications were applied just for severe PONV and definition of severe PONV?
Line 21. „.....(hydromorphone <2mg) with without ...“ with or without ?

Correction made
Line 22. „Patients who received general anesthesia by use an airway device other than ETT or LMA....“ Who made selection of AD applied? I hope it would not be redundant to write that decisions regarding airway management were left to the discretion of attending anesthesiologists. What were their criteria for decision: LMA or ETT? Anesthesiologists preferred ETT for longer lasting surgical procedures like in this study and it is known that experienced anesthesiologists prefer LMA while less experienced prefer ETT. Moreover, published data suggested long term learning curve with LMA usage (Brimacombe J. Anaesthesia 1996; 51:76-80). It would be nice to know how many of anesthesiologist were training or senior? Further, position of the patient during surgery could influence on decision to choose ETT or LMA and might have some influence on final results of the study. Let us know if all patients were in supine position!

All patients were in supine position and decision to choose the airway device was made by attending anesthesiologist.

Line 24. “….shorter than 15 minutes or longer than 240 minutes...“ Are there special reasons to choose 15 and 240 minutes as time limitations for duration of surgery or it was voluntary? Actually, some authors have suggested that use of LMA >2h may increase risk for aspiration (Asai T, Morris S. Can J Anaesth 1994; 41:930-60)

The spread of our data was mostly between 15 to 240 minutes. Very few outliers.

How long patients stayed in PACU and how long in hospital? Put here that you followed them for PACU stay only and that some patients were outpatients and other stayed in hospital for at least ...... Predictors for PONV are not the same for inpatients and outpatients.

We followed patients for 8 hours. Most patients were ambulatory.

4. Results.
Page 6.
Line 2. „...was 10.5%...“ put here „51/497 (10.5%)..“ and so on....through the entire section because of different size groups.
Correction made

Line 3 ...“when corrected for the use of N2O....“ What exactly does it mean? How did you make such correction? (explain this in methods)
Correction made.

How many patients in ETT subgroup with N2O had PONV and how many of
them had PONV in ETT subgroup without N2O and was difference significant？(P value)? How many patients in group LMA subgroup with N2O experienced PONV and how many in the same group but subgroup without N2O (was it significant difference)?

Correction made.

Line 9/10 „prophylactic antiemetic …..P<0.01“ Actually, P=0.13 in the table 3. Is it mistake?
P=0.13 correct

Line 11 „The data was again divided and length of surgery was assessed.“ This sentence is unnecessary in the result section. Deleted.

5. Tables
Table 1. Title „post-operative nausea.“ Add vomiting „postoperative nausea and vomiting „
correction made.

There are much more males than females 454 vs 43 and percent values are needed (%).corrected.

Smoking status ….P value missed.
Ex smoker definition as well as all perioperative events and „P<0.05 was statistically significant“ are needed to add under the table.
Table 2. Antiemetic „Any“…list all antiemetics that were chosen under the table as well as NMB reversal agents.
Table 3 delete „for the choice of airway“ and change to „Demographic characteristics and perioperative data.“
Put here not only N but percent values!
Add here risk score for PONV according to simplified Apfel's predictive model or other which you practice for PONV prophylaxis! Assessment of risk for PONV would be of a great value when two groups, ETT vs LMA, were compared.

All correction made.

Line 17. add here nitrous oxide (yes/no) because some patients in each group received it
Line 26. „Any periop. events…“ Rather make next another table with perioperative events in both groups (ETT and LMA) as well as rescue antiemetics, PONV and pain (for example opioids: yes/no)
Put definition of the perioperative events under the table. Also, applied medications and values for antiemetic rescue treatment (N, %) are needed.

Corrected.
6. Discussion

Page 7

Line 5 „We conducted this study to demonstrate an associated increase of PONV with the use of ETT in comparison to LMA.“ Actually, the aim of this study was to find whether LMA vs ETT usage during anesthesia has influence on PONV. Authors proposed that patients with LMA have increased frequencies of PONV based on previous study where researchers have been suggested that higher barometric changes in MEP gradient in the nitrous oxide treatment group was associated with higher frequencies of PONV (Nader ND et al. Laryngoscope 2004;114:883-6).

Corrected

Line 6/7 „Our finding does not correlate with the trend towards increased changes in middle ear pressure with LMA seen in earlier publication by our group. Here we did not look at MEP gradients.“ If you did not measure MEP it sounds little confused to correlate your result with changes in MEP by Nader et al. Actually, middle ear pressure was not measure here but Nader et al. measured it in patients with ETT and LMA and found significant increase of MEP gradient and PONV incidence when LMA with nitrous oxide was used during anesthesia.

It is true it was corrected

Line 8 „....., information obtained from our data does not determine the cause of PONV,.....“ Rather change „Since PONV is multifactorial in its origin,.....“ Corrected.

Line 11 „.....when variables were mached.“ May you list here all that variables and shortly explain in method section (statistical analysis) how did you mach variables?

Deleted.

Line 12 „There was significantly greater risk of PONV in patients who had an ETT ...“ What is the main explanation for this final result? How many patients in ETT group used N2O and in which concentrationes in comparison with LMA group? It is important to know that because N2O is known as emetogenic agent. Once again, because of confounding factors you need comparison of these two groups according to predictive model for PONV, for example Apfel's if you use it in your anesthesia practice.

Sinclair score was used and number of patients explained in the table.

Line 20 „...Many of the surgeries recorded in our study were of shorter time frame“
It would be nice to put a number (in parentheses) of surgeries lasting less than 1 hour in this study?

65.7% of cases were less than 60 minutes.

Page 7 Line 25/ Page 8 Line 1, “Perhaps the finding in our study also represent a subset of patients where N2O is not a risk factor ...“ rather use predictor than risk factor ....“...for PONV, namely patients where a LMA is used.“ change "is" into "was". Have you been analyzed your data at least preliminary before you claimed this?

Corrected.

Page 8
Line 6 „...but the trend between the findings is the same.“ May you illustrate this claim to us?
Deleted.

Page 9
Line 1 „.....we excluded patients receiving doses of greater than 3mg ...“ As mentioned above there is constant doubt that doses of neostigmine 2.5 mg or higher might contribute to higher incidence of PONV. Numbers needed to treat to prevent emesis by omitting neostigmine compared with using it were consistently negative with 1.5 mg and consistently positive (3-6) with 2.5 mg. (Tramèr MR, Fuchs-Buder T. Br J Anaesth 1999; 82: 379-86.) All exclusion criteria must be written in methods section.

Corrected.

Have you any comments about other findings such as ASA PS, type of admission and so on....
No

7. Conclusion.
A prospective, randomized, placebo controlled study would give more accurate answers about the effect of AD on PONV than retrospective study biased by confounding factors.

ADDED TO conclusion
Response to reviewer two:

This is a retrospective study assessing the impact of the choice of airway device on the incidence of PONV in patients undergoing knee surgery under general anesthesia. The incidence of PONV was higher with the use of ETT. However, patients in the ETT group had significantly higher risk for PONV: more females, underwent longer surgeries and received NMB reversal with neostigmine. Other risk factors such as history of PONV/motion sickness and smoking status are not reported for the ETT vs. the LMA groups. Use of N2O in the two groups is also not reported. When the authors performed a multivariable analysis, the only independent risk factors for PONV were gender and N2O. Therefore the conclusion that airway device impacts PONV is not justified; patients in the two groups did not have the same baseline risk for PONV.

We appreciate the important comment from reviewer #2 and have reported history of PONV and smoking for both groups and performed propensity matching for both group in the tables (reported). Also Sinclair risk score was added to the result and method.

Abstract:
Page 1, results: how about the use of N2O in the LMA group, either report both groups or only the overall study sample as you have already done.

We used N2O in both group at 50% only.

Introduction:
The aim of the study is not clear “to assess if selection of airway device was associated with the incidence of N2O-mediated PONV..”, please reword.

The aim of the study was rephrased

Methods:
Are the charts in your institution electronic or manual? Electronic charts
What were the types of knee surgery included? Knee arthroplasty
How did you identify pre-existing nausea or vertigo? Are these variables routinely collected on all patients preoperatively? Definition provided and information is routinely collected at the preop clinic (template).

The sentence “The incidence of PONV as assessed and recorded…" is not complete.
You limited the antiemetics to metoclopramide, ondansetron and dexamethasone, is there a possibility that other antiemetics such as promethazine, and scopolamine for instance could have been used?

We do not use scopolamine and promethazine in our hospital.
How did you define baseline blood pressure? How complete was the recording of adverse events as you describe?

There are other important covariables that should have been included in the multivariable model such as opioid consumption and risk factors for PONV such as history of PONV/history of motion sickness, and non-smokers.

We did univariate analysis with matching and also multivariate analysis without matching using historical risk factors for PONV such as opioid consumption and risk factors for PONV such as history of PONV/history of motion sickness, and non-smokers.

Results:
What is meant by “data was matched for age, gender,...” do you mean controlled for those variables in the model?

we mean data were controlled ....

The most important part of the analysis is the multivariable model; please report the details? See explanation above and the method section.

Table 3: Please report the use of N2O in the two groups.?

N2O Was limited to 50% only and numbers reported.

Sincerely Yours,

Jahan Porhomayon, MD,FCCP