Author’s response to reviews

Title: Comparison of surgical field visibility during propofol or desflurane anesthesia for middle ear microsurgery

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Author’s response to reviews:

Dear Editors,

We read carefully the comment from the reviewers. We made the point to point revision according to the comments from you and the reviewers. We highlight the changes in red.

David M. Polaner (Reviewer 1)

1. Although a statistical difference between groups was measured, the clinical difference between them was minimal. The authors note this in the discussion p9, l47-57), however this important result is notably absent from the final conclusion. I think that it should be added - such a qualifier (that when remifentanil is used in combination with desflurane similarly acceptable operative conditions can be achieved) is pertinent to the final conclusion.

Answer: Thanks for you thoughtful advcse. We add the sentence to the final conclusion “When remifentanil is used in combination with desflurane similarly acceptable operative conditions can be achieved.” Please see page 10, the Conclusion Section.

2. Other major comments:

1). p10, 118: I do not believe this is correct. It is more likely that the reduced remifentanil requirement in the desflurane group was due to the far more potent analgesic contribution of
desflurane compared with propofol, which has primarily sedative hypnotic (and minimal analgesic) effects.

Answer: Thank you for the advice. We revise the sentences as “However, patients in the DR group required less remifentanil than those in the PR group, it is more likely that the reduced remifentanil requirement in the desflurane group was due to the far more potent analgesic contribution of desflurane compared with propofol, which has primarily sedative hypnotic (and minimal analgesic) effects. please see page 10.

2). Middle ear microsurgery for cholesteatoma is a common operation in children as well as in adults. I suggest adding a sentence in the limitations section noting that, and due to the study population these results are limited to adults and might require further confirmation in children. (I am revealing my bias as a pediatric anaesthetist here!).

Answer: We add the sentence “ Due to the study population these results are limited to adults, the findings in our study might require further confirmation in children. “ in the limitations section. Please see page 10.

3). In figures 2 and 3A and B I suggest eliminating the connecting lines between data points. Your data here are actually discreet and categorical, not continuous, and the lines connecting the points suggest that you are displaying the intermediate values measured between those points. Certainly there were intermediate clinical measurements during those periods, but those data points were neither collected nor analysed in the study, so it is best not to imply that there was a continuous transition between the time points unless they were in fact analysed.

Answer: Thanks for you comments. We remove the connecting line in Figure 2. The data are now expressed as mean (error) (95% CI). As for hemodynamic profiles, we intended to observe the trend of hear rates and mean blood pressure during the operation, so the connecting lines were kept in Figure 3A & B. If you prefer removing the lines, we would be happy to make the changes.

3. Minor comments:

1). pdf p5, l28: To more completely define the patient population I suggest modifying this to read "Adult patients".

Answer: We now define the population as “adult patients”. Please see Abstract Section and Method Section.
2). p6, l25: Please clarify if the hydromorphone was consistently given at the end of the anesthetic for postoperative analgesia only, or if it contributed to the intraoperative opioid load in some patients (the former is implied, but not explicitly stated)

Answer: We now make it clear that hydromorphone was consistently given at the end of the anesthetic for postoperative analgesia only. Please see page 5, Methods Section.

3). p6, l40: It would be helpful to the reader unfamiliar with the Boezaart scale to add a phrase at the end of this sentence "where 0 denotes the best and 5 the worst visibility", especially since the meaning of the score's magnitude is not immediately intuitive (one would expect a higher score to imply better visibility). I would not change the sentence on p7 l10, however, as this reminder further enhances the clarity.

Answer: Now the sentence is revised as “Attending surgeons who were blind to treatment group rated surgical field visibility from 0 to 5 according to the Boezaart grading scale where 0 denotes the best and 5 the worst visibility. “Please see page 6, Methods Section.

4). p8, 147-49: I know that you have defined the abbreviations "PR" and "DR" at their first mention in the beginning of the manuscript, however it is my personal preference (and I leave it to the editor to agree or disagree with me here) that in the first sentence of the discussion, where the primary outcome result is stated, to spell these out.

Answer: We define the abbreviations "PR" as propofol/remifentanil and "DR" as desflurane/remifentanil at their first mention in Discussion Section. Please see page 8.

5). p8, 154-57: the opening phrase of this sentence is redundant; you can simply begin the sentence "This confirms previous findings that…".

Answer: We revise the sentences as follow: This confirms previous findings that propofol anesthesia allows better surgical field visibility and less blood loss than inhalation anesthesia. Please see page 8, Discussion Section.

6). p9, l8-10: One might consider adding a phrase to the end of this sentence noting that these findings suggest that when well controlled, heart rate itself is not the determinant of operating conditions and that other mechanisms (as you discuss below) are in play. p9, l30: I would delete the word "combination"
Answer: We add the sentence “These findings suggest that when well controlled, heart rate itself is not the determination of operating conditions and that other mechanisms are in play.” in the second paragraph in Discussion section. We delete the word “combination”. Please see page 8, Discussion Section.

Togay Müderris (Reviewer 2)

It is a well organized and written manuscript on an interesting topic.

Answer: Thanks for you confirmation in our work.

Smita Prakash (Reviewer 3)

1. Major concerns:

1). As remifentanil consumption in PR group was considerably higher, 850 μg versus 258 μg, how have the authors concluded that PR anesthesia is superior to DR anesthesia in terms of better surgical field visibility? The superior surgical field visibility conditions were likely the result of increased remifentanil usage in PR group.

Answer: In our study, we found that the Boezaart grading scales (0 denotes the best and 5 the worst visibility) were lower in the PR group which means the surgical conditions were better in PR group. So far, we do not know the exact mechanism underlying the difference of surgical condition. We agree that increased remifentanil usage in PR group might contribute to the better surgical visibility. We add this to the Discussion Section, Please see page 10.

2). The effect site concentration for remifentanil in the two groups is different. To clearly prove that PR is superior to DR, the effect-site concentration of remifentanil in the two groups should have been kept same. Degoute et al found that remifentanil combined with propofol enabled controlled hypotension, reduced middle ear blood flow and provided good surgical conditions for tympanoplasty. They reported reduction in middle ear blood flow in a range of 25% and dryness of the operative field obtained by a reduction in HR, BP and microcirculatory autoregulation. It is possible that the difference in remifentanil requirement between the two groups is responsible for better surgical field visibility scores in PR group compared with DR group.

Answer: In our study, there was significant difference in terms of remifentanil dosage between the two groups. We agree that better surgical condition in PR group may be due to higher
remifentanil dose that leads to reduced middle ear blood flow as reported by Degoute et al. In our further research we would like to evaluate the surgical conditions by keeping the same effect-site concentration of remifentanil in the two groups.

3). How was blinding of the surgeons achieved?

Answer: The surgeons were blinded to the anesthesia type by shielding the vaporizer and propofol and remifentanil syringes. We add this sentence in the Method Section. Please see page 5.

4). Please write the study hypothesis in Introduction.

Answer: We hypothesized that propofol/remifentanil anesthesia may provide better surgical condition than desflurane/remifentanil anesthesia during middle ear microsurgery. Please see page 4, Introduction Section.

2. Abstract:

1). Please state the number of patients studied.

Answer: A total of 80 adult Patients undergoing middle ear microsurgery due to cholesteatoma otitis media with American Society of Anesthesiologists physical status I and II were randomly assigned to the PR or DR groups.

2). Please write American Society of Anesthesiologists physical status I and II.

Answer: Corrected as above.

3). Please write remifentanil consumption mean (range).

Answer: Since the data of remifentanil did pass the D'Agostino & Pearson normality test, we describe the remifentanil dose by using median (first/third quartiles).

4). Brief methodology may be mentioned in abstract.
Answer: Brief methodology is described as: A total of 80 adult Patients undergoing middle ear microsurgery due to cholesteatoma otitis media with American Society of Anesthesiologists physical status I and II were randomly assigned to the PR or DR groups. The depth of anesthesia was titrated to maintain a Bispectral index (BIS) between 40 and 50. Remifentanil was titrated to maintain the mean blood pressure within ±30% change of the pre-induction value. Surgical conditions were rated at several timepoints by the surgeons using the Boezaart scores. Please see Abstract Section, page 2.

3. Introduction

1) Page 3, line 22: "changes to general anesthesia" this is not clear. Please clarify or else delete

Answer: We change the phrase “changes to general anesthesia” into “manipulation of general anesthesia.” Please see page 3, Introduction Section.

2) Page 3, line 34: "consistent with findings that surgical scores..." Please clarify which scores are being referred to here.

Answer: We revised the sentence as “Consistent with findings that surgical conditions are correlated with intraoperative heart rate rather than mean blood pressure.” Please see page 3, Introduction Section.

3) Page 4, line 28: please write ASA as above

Answer: We revise the sentence as “Adult patients with American Society of Anesthesiologists physical status I and II scheduled for middle ear surgery due to cholesteatoma otitis media were consecutively recruited.” Please see page 4, methods Section.

4) Page 4, line 34: please be specific with regard to exclusion criteria

Answer: Patients were excluded if they were receiving cardiovascularly active drugs or drugs related to coagulation (e.g., warferin, heparin, enoxiparin, NSAID or aspirin). Please see page 4, Methods Section.

5) Page 4, line 40: please consider writing as: Upon arrival to the operating room, non-invasive blood pressure, pulse oximetry, .....BIS monitoring was established.
Answer: We revise the sentence as “Upon arriving to the operating room, non-invasive monitoring of arterial blood pressure, pulse oximetry, electrocardiography, and bispectral index (BIS) monitoring (BIS VISTA Monitoring System; Aspect Medical Systems, Inc., Norwood, MA, USA) was established.” Please see page 4, Methods Section.

6). Page 4 line 54: Please write complete drug names

Answer: We complete the drug name “Patients were randomly assigned to the propofol/remifentanil (PR) or desflurane/ remifentanil (DR) group by computer-generated allocation.” Please see page 4, Method Section.

7). Page 4 line 54: Please clarify whether maintenance was with oxygen in air or oxygen and nitrous oxide

Answer: Patients received mechanical ventilation in pressure-controlled mode with a tidal volume of 8 ml/kg at a rate of 10 breaths per min to provide an end-tidal CO2 concentration of 35–45 mmHg. The carrier gas flow for both groups consisted of oxygen and air (FiO2 0.5) during anesthesia maintenance. Please see page 5, Methods Section.

8). Page 5, line 40: Please describe Boezaart grading scale.

Answer: Attending surgeons who were blind to treatment group rated surgical field visibility from 0 to 5 according to the Boezaart grading scale where 0 denotes the best and 5 the worst visibility. Please see page 6, Methods Section.

9). Page 5 line 47: Do the authors mean 10 minutes after skin incision?

Answer: We revise the phrase “10 minutes after surgery “ as “10 minutes after skin incision.”

10). PACU time is described as between end of surgery and Aldrete score>9. It should be described as between extubation or arrival in PACU till Aldrete score....

Answer: The sentence is now expressed as “PACU time (time between extubation and achieving a modified Aldrete score[13] > 9.” Please see page 6, Methods section.
4. Results

1). Page 7 line 13: please write exact p value instead of P<0.05.

Answer: The exact p value is P = 0.001.

2). Page 7 line 35: Table please give ref for ephedrine requirement.

Answer: Ephedrine was needed for any decrease in mean blood pressure lower than 30% from the patient’s pre-induction value.

3). Page 7 line 5: surgery scores... please clarify

Answer: We revise the phrase “surgical scores” as “surgical conditions”

4). The authors mention that average propofol effect site concentration mcg/ ml 3.4(0.6). What was the average remifentanil effect site concentration? Please mention in results

Answer: The median (first/third quartiles) remifentanil effect site concentration were 3.6 (2.8/5.0) ng/ml in PR group and 1.7 (1.0/1.6) ng/ml in DR group, P < 0.0001. We add the results in the Result Section, as well as in Table 2.

5. Discussion

1). Page 8 line 23: This has been stated for the first time in discussion and should be mentioned in results too.

Answer: The mean propofol site effect concentration was 3.4 μg/ml. The mean desflurane MAC was 0.8. Please see Result Section, page 8.

2). Page 8 line 40-47: Not clear, please clarify. The authors may also compare their results with those of other studies on the subject.

Answer: We rewrite this paragraph as follow: We routinely use remifentanil during middle ear surgery in our clinic because of its analgesic effect and reduction of middle ear blood flow, consistent with Degoute et al.[15,16]. Degoute et al. found that remifentanil/propofol anesthesia was effective in reducing middle ear blood flow and providing good surgical conditions for adult patients during tympanoplasty in a small sample study[15]. Later they found that when combined with sevoflurane, an inhalation anesthesia, remifentanil enabled controlled hypotension, reduced
middle ear blood flow and provided good surgical conditions for middle ear surgery in children[16]. In our study, although PR anesthesia produced better surgical field visibility than DR anesthesia, average surgical field visibility score was <2 under DR anesthesia, indicating good surgical conditions. These findings suggest that DR anesthesia is applicable for middle ear surgery and can explain why, in our otology surgical center, surgeons seldomly complain of impaired surgical visibility during desflurane usage. Please see page 9.

Kumar Belani, MBBS, MS (Reviewer 4)

The authors have attempted to evaluate surgical field visibility during middle ear surgery for cholesteatoma. Consenting patients were randomized and the surgeons were blinded. The patients were divided into two groups of 40 each - 1 group received propofol as the main anesthetic and the other received desflurane. Remifentanil was used for both groups. Both groups received ondansetron and dexamethasone for PONV prophylaxis. At one point during the surgery the authors report that surgical field visibility was significantly better in the propofol group. The following needs explanation:

1. The numbers are too small to make this as a far reaching conclusion. With larger numbers would the surgical field would have been scored better earlier on in the propofol group?

Answer: The overall surgical field visibility scores were lower in the PR group and the difference was only statistically significant at one time point (during lesion clearance). We agree that with larger numbers would the surgical field would have been scored better.

2. What was the reason tachycardia was not observed in the desflurane group?

Answer: In our study we did not observe significant tachycardia in the DR group. The reasons may be as follow: First, desflurane tends to stimulate circulation (i.e., increase heart rate) at high concentration (over 1 MAC), the concentration of desflurane in our study was 0.8 MAC. Second, as opioids can eliminate the stimulatory effect of desflurane on the circulation system, remifentanil use might have eliminated tachycardia in the DR group. We explained this phenomenon in discussion section, page 9.

3. How come the incidence of PONV was similar in both groups?

Answer: First, we only observe the PONV episode during PACU stay, there was possibility that we underestimated the incidence of PONV. Second, 0.15 mg/kg ondansetron hydrochloride and 0.1 mg/kg dexamethasone were given to prevent PONV in our study. Third, The sample size was not large enough to detect the difference between the two groups.
4. Since there is less vasodilation with propofol as compared to desflurane as the authors indicated, did the surgeons find more bleeding (microscopic) in the desflurane group?

Answer: As we discussed, we found that the average surgical field visibility score was <2 under DR anesthesia, indicating good surgical conditions. These findings suggest that DR anesthesia is applicable for middle ear surgery and can explain why, in our otology surgical center, surgeons seldomly complain of impaired surgical visibility during desflurane usage. Please see Discussion Section, page 9.