Author's response to reviews

Title: The effect of cigarette smoking on washout time of sevoflurane anesthesia

Authors:

Tayfun Adanir (tadanir@tnn.net)
Aynur Atay (atayaynur@mynet.com)
Atilla Sencan (atiillasencan2000@yahoo.com)
Murat Aksun (murataksun@yahoo.com)
Nagihan Karahan (karanhang@yahoo.com.tr)

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Author's response to reviews: see over
Dear Editor,

We have revised the manuscript entitled “THE EFFECT OF CIGARETTE SMOKING ON WASHOUT TIME OF SEVOFLURANE ANESTHESIA” (MS: 6168010931126155) in light of the reviewers’ comments and the followings are the point to point clarifications:

**Reviewer 1:**

Minor Essential Revisions
1. The title should be changed: recovery is not measured here, but the washout time.
   
   We changed the title.

2. One MAC-h standardized sevoflurane anesthesia: this refers to exact 1 MAC-h anesthesia. However, in study design it is said: "On average, operations lasted 1 hour." Please clarify, whether sevoflurane exposure was exactly 1 MAC-h or, 1 MAC-h 'on average'.

   We clarified this misunderstand issue in the text.

3. There seem to be a tendency toward shorter washout times for smokers compared to non-smokers, although clinical significance was not reached. Unfortunately, the description of sample size evaluation is missing, and should be included.

   Sample size evaluation and limitations of the study were stated in the text (in statistical analysis section and discussion section).

Discretionary Revisions
The figures, as they are, do not really add anything for the report. Their information could easily be included in the text.

We don’t agree with this idea. Because, the figures have more visual impact.

**Reviewer 2:**
In this interesting study the authors evaluate the impact of smoking on the washout time of sevoflurane anesthesia. The study is well designed resulting in useful conclusions. Despite the very important messages the authors have to response to the following remarks.

1. Which is the power of the study that defines the number of patients included.

Sample size was stated in the statistical section.

2. Even if smoking can many fold increases the function of P450 pathway, hepatic metabolism of sevoflurane is approximately 3% that is virtually considered quite low to affect washout kinetics of this volatile agent. Please comment.

We agree with you. For this reason, we discussed the issue in the discussion section.

3. Refer more studies from the literature about the impact of smoking on the metabolism of other volatile anesthetics.

The studies from literature about the effect of smoking on the metabolism of other volatile anesthetics were stated.

4. This report seems to have an awkward writing style, with many grammatical stylistic challenges. English support and grammatical corrections will be important if this manuscript is accepted.

The manuscript was revised for English grammar.

Reviewer 3:

General Comment
The authors need to be consistent in the use of smokers, smoke, tobacco smoker, cigarette smoker. Generally, it is best not to have “smoke” without a modifier. I would prefer the use of either “tobacco smoke” or “cigarette smoke” throughout the manuscript. Which ever the authors’ choose should then be used consistently throughout. However, the use of “smokers” or “smoking” is clear to me and does not need to be accompanied by a modifier.

We used “cigarette smoking” throughout the manuscript.

Abstract
Background: Smoking tobacco does more than affect metabolism of drugs via induction of the P450 system. As the authors discuss in the paper it also affects pulmonary mechanics. In a drug such as sevoflurane, where the primary route of elimination is via the lungs, the pulmonary affects of chronic smoking may predominate in any effect on the elimination of sevoflurane. The first sentence of this abstract should also state such as effect as a theoretical mechanism of impaired sevoflurane washout among smokers.

Methods: State smokers did not have significant pulmonary disease. State patients were mechanically ventilated during the washout time.
Conclusion: Eliminate the first sentence. Would reword the second sentence to “Washout time of sevoflurane does not appear to be effected by smoking in patients without significant pulmonary disease”

According to the Reviewer, The abstract section was revised.

Background
First, we all know that smoking is a problem world-wide and that smoking has many bad general implications for the anesthesiologist, but these are generic concerns and not germane to your study. Delete those statements and focus on evidence (if any) that smokers may have problems with volatile anesthetic washout. Why are you concerned about this topic? Has there been interference of washout with more soluble volatile agents such as halothane in smokers, etc.?
Second, the current organization of these two paragraphs is confusing, the text jumps from idea to idea and back again in the first and second paragraph. You propose 3 possible general mechanisms by which smoking can alter washout times: impaired lung function, induction of the CYP2E1 system, and changes in the CNS response to anesthetic agents.
Third, provide references for the CYP2E1 and changes in the CNS response. Lastly, expand on how smoking affects parameters of lung function (diffusion, obstruction) rather than on mechanisms (activation of neutrophils).

We revised the background section.

Methods:
Patients paragraph: Change to 30 life-long non-smokers and 30 smokers from “smoking”. Provide details how you assessed that non-smokers were indeed life-long non-smokers (given the very high rates of smoking in Turkey). How did you assess that smokers smoked more than a pack a day? Did you assess how long smokers have been smokers?

We explained how we assessed that non-smoker and smoker in the methods section.

One could argue that smokers have pulmonary disease. How did you assess that patients did not have pulmonary disease? Was this a clinical assessment, did patients have pre-operative chest x-ray, pulmonary function tests? Please provide these details, and depending upon those, update your limitations section in the Discussion.

The relatively healthy smokers were chosen. We explained how assessed the patients in the methods section. The limitations of the study were stated in the discussion section.

The last sentence of the first paragraph is confusing, do you mean patients with preexisting pulmonary disease, cardiac disease, hepatic disease, renal failure or do you mean pulmonary failure, cardiac failure, hepatic failure. Revise and clarify.

The sentence was revised and clarified.

Study Design:
General comment: Justify your study design by providing references of previous washout studies.

First paragraph of study design:
Patients were not allowed to smoke day of surgery?

3rd sentence: simplify by stating that “in addition to standard ASA monitors the following” was monitored and include what else you monitored.
Change fresh gas flow to 4 l.min-1

Statement: “On average, operations lasted 1 hour”, consider eliminating and under

Patients section add “hour long otorhinolaryngologic elective surgical procedures”

Was ventilation standardized during the surgical procedure? If not, any general parameters that could be offered?

Second paragraph of study design:
Clarify that you were maintaining mechanical ventilation until extubation and that this was standardized based on ideal body weight. State patients were extubated after the last measurement.

Just a comment, remifentanil does not prevent recall.

All above the comments were stated in the study design section.

Results
Make this into one paragraph. Please provide P values rather than >0.05.
Make the last sentence the second sentence.

We remedied these suggestions.

Discussion
Summarize your study’s findings as the first statement. Also, please explain the meaning of both washout time and Fi/Fexp ratio here. Then discuss the Mendonca paper in this section. Are there any reports in the literature that smoking does effect elimination of volatile anesthetics? If so, please summarize previous reports here. Is there a difference in your findings compared to previous work? If so, please discuss as to why there are inconsistencies in findings.

The overall organization of the Discussion is poor and jumps from subject to subject as in the Introduction. Organize it into the three general proposed mechanisms as to how smoking may effect sevoflurane elimination, and why you do not think this was a factor in your study. You also need to better reference statements in the discussion. Provide a limitations section addressing that your findings may not apply to smokers with lung disease. Also state if you did not obtain preop PFTs on patients, that you may have missed occult lung disease in smokers. Also, some studies of this nature obtain plasma levels of volatile anesthetics, which might provide more accurate data, state this as a limitation. Do you think results would be similar if this study was performed with more and less absorbable volatile agents (halothane vs desflurane)?

Conclusion statement: You cannot conclude from your study what effects, if any, smoking has on the metabolism of sevoflurane. If the literature speaks of this, then you should state this in your reasons for performing the study in the first place. But as you discuss there are several mechanisms by which smoking may affect MAC of sevoflurane. The only thing you can conclude is that washout time was not effected in healthy (relatively) smokers. Delete the first sentence of this statement. Consider rewording the second sentence so it is not a repeat of the abstract.
We remedied all the above suggestions.

Table 1
Provide P values to two digits. Be consistent with the number of digits used to describe means and standard deviations. With years, unless you calculated years to the birth date to year of surgery (and there is no reason to do this in adult patients) I usually provide a whole number for the year. (i.e, 40 +/- 11 vs 42 +/- 11, P = 0.XX).

P values were stated with two digits. Patients’ ages were written according to the reviewer’s suggestion.