Author's response to reviews

Title: Consumption of Cisatracurium in different age groups, using a closed loop computer controlled system.

Authors:

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Version: 2 Date: 30 October 2013

Author's response to reviews: see over
Reviewer 1#
Reviewer's report
Title: Consumption of Cisatracurium, Sufentanil and Propofol in different age groups, using a closed loop computer control system.
Version: 1 Date: 7 May 2013
Reviewer: JENNIFER M HUNTER
Reviewer's report:
The authors report on the use of an infusion of cisatracurium together with propofol and sufentanil in three different age groups. The article is written in reasonably good English and the relevant literature is well reviewed.

I would make the following major comments:
1. Although the methodology in this paper is sound, the findings are not especially new, as reference 16 in the text exemplifies.
2. In the Caucasian races, it is usual to study an elderly group over 75 years, as the physiological changes of ageing described in the Discussion do not tend to be marked until this age. If the authors consider there to be a difference according to ethnicity in this respect, it should be considered in the Discussion section and is worthy of further research.
3. It is inappropriate to provide details of the cisatracurium consumption to three decimal places - at most, only two should be given throughout the text.
4. In the Abstract and throughout the paper, you must define in terms of the TOF count or TOF ratio, what you mean by recovery period and recovery index.
5. It should be acknowledged that the monitoring methods used for adjusting the dose of sufentanil and propofol are very clinical and not necessarily accurate.

MINOR POINTS
1. Make sure that you have put all the references in the correct format for the journal you have submitted your manuscript to, and that the format is consistent..

Level of interest: An article of limited interest
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 1#
Point 1: Although the methodology in this paper is sound, the findings are not especially new, as reference 16 in the text exemplifies.

Response: Thank you so much for your good suggestion. As per your reminder, we carefully read the reference 16 again. We found that there are some differences between this reference and our paper: first, the criteria of grouping are different. In their paper, they divided patients to young (18-50 yr) and elder (> 65 yr) groups. The
young group in their paper included young (18-45 yr) and middle-aged people (46-50 yr). In our paper, we divided patients into three groups, those are young (20-45 yr), middle-aged (46-64 yr) and elder (> 65 yr) people. The classification of age is more detailed in our submission. Second, the method we used for infusion of cisatracurium is different from theirs. In our paper, we used a computer controlled closed-loop infusion system (CLMSRI-I, Guangxi VERYARK Technology Co., Ltd.) for the infusion of cisatracurium, which maintained a neuromuscular blockade of 90% during operation. The advantage of this infusion system is to provide a stable intra-operative level of neuromuscular blockade. In their article, the cisatracurium (0.1 mg/kg) was administered over 5 s, and the additional doses of cisatracurium were administered as the T1/T0 recovery at least 25%. If more than 2 or 3 additional doses were required then cisatracurium was infused at 3 μg·kg⁻¹·h⁻¹, adjusted to maintain a detectable twitch response (Sorooshian SS et al. Anesthesiology. 1996, 84(5): 1083-1091). As compared with intermitted bolus or continuous infusions of neuromuscular block, the advantage of closed-loop control system is that it composed of a personal computer, a neuromuscular block monitor and a syringe pump and could seek the best infusion rate in any operation situations if the monitor is reliable during surgery. Furthermore, closed-loop drug therapy offers considerable benefits in patient care by providing the ability to maintain stable neuromuscular block while allowing for variations in individual response to the drug. Cisatracurium is more suitable for closed-loop infusion because it is a kind of neuromuscular blocker agent with longer onset time, which makes it more difficult to control the reduction (Chuang CTSE et al. Biomed Eng Appl Basis Comm. 2006, 18: 284-295.). Third, the general anesthetic used in the reference 16th is different from ours. In their paper, they used isoflurane combined with nitrous oxide and fentanyl to maintain the general anesthesia. However, in our submission, we used propofol combined with sufentanil. Jellish et al. found that isoflurane enhanced prolonged cisatracurium T (1) 75% recovery as compared with propofol anesthesia. Therefore, the different combination of agents could affect the pharmacokinetics and pharmacodynamics if cisatracurium (Anesth Analg. 2000, 91(5):1250-1255). Fourth, as per the results, we calculated the consumption of
cisatracurium, sufentanil and propofol, the recovery index (defined as time for TOF to increase from 25% to 75%), those are not showed in the paper of Sorooshian et al. These are the differences between our paper and reference 16th. Thank you so much for your careful consideration and reminder, we still think we should learn the scientficity and preciseness from this reference.

**Point 2:** In the Caucasian races, it is usual to study an elderly group over 75 years, as the physiological changes of ageing described in the Discussion do not tend to be marked until this age. If the authors consider there to be a difference according to ethnicity in this respect, it should be considered in the Discussion section and is worthy of further research.

**Response:** From the government website of WHO (http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html), we found the “Definition of an older or elderly person” is “The ageing process is of course a biological reality which has its own dynamic, largely beyond human control. However, it is also subject to the constructions by which each society makes sense of old age. In the developed world, chronological time plays a paramount role. The age of 60 or 65, roughly equivalent to retirement ages in most developed countries, is said to be the beginning of old age. In many parts of the developing world, chronological time has little or no importance in the meaning of old age. Other socially constructed meanings of age are more significant such as the roles assigned to older people; in some cases it is the loss of roles accompanying physical decline which is significant in defining old age. Thus, in contrast to the chronological milestones which mark life stages in the developed world, old age in many developing countries is seen to begin at the point when active contribution is no longer possible.” (Gorman M. Development and the rights of older people. In: Randel J, et al., eds. The ageing and development report: poverty, independence and the world's older people. London, Earthscan Publications Ltd.,1999:3-21). In a review of Cope et al., they stated that the physiological changes such as the decrease in cardiac output and muscle mass, an increase in body fat and the deterioration in renal and hepatic function, which could affect the
pharmacokinetics of neuromuscular-blocking agents may not become apparent clinically in healthy individuals until the age of at least 75 years (Drugs Aging. 2003, 20 (2): 125-140.). In the study, the average age in the elder group is 73.6±3.2 yr (please see the table 1 which submitted as Additional File), which is very close to 75 years of age. Thank so much for your good suggestion, as per your reminder, we have added the explanation of this in the Discussion (please see page 9, line 4-10).

Table 1. The demographic data and results of the three groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1(20-45)</th>
<th>Group 2(46-65)</th>
<th>Group 3( &gt;65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Age</td>
<td>38.0±7.0</td>
<td>54.7±4.5</td>
<td>73.6±3.2</td>
</tr>
<tr>
<td>Weight</td>
<td>67.1±8.6</td>
<td>67.6±10.5</td>
<td>61.2±14.4</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3±2.16</td>
<td>24.7±3.2</td>
<td>21.8±1.8</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/14</td>
<td>12/21</td>
<td>6/14</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>1.767±0.318</td>
<td>1.622±0.378</td>
<td>1.297±0.393</td>
</tr>
<tr>
<td>consumption, µg/kg/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery Index</td>
<td>8.81±2.6</td>
<td>11.48±2.9</td>
<td>12.7±2.5</td>
</tr>
<tr>
<td>minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.44±0.14</td>
<td>0.38±0.11</td>
<td>0.30±0.05</td>
</tr>
<tr>
<td>consumption, µg/kg/hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>5.05±0.4</td>
<td>4.28±0.6</td>
<td>3.07±0.5</td>
</tr>
<tr>
<td>consumption, mg/kg/hr</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Point 3:** It is inappropriate to provide details of the cisatracurium consumption to three decimal places - at most, only two should be given throughout the text.

**Response:** Yes. We totally agree. We have revised these in our submission (please see page 2, line 13-14; page 7, line 6-7). Thank you!

**Point 4:** In the Abstract and throughout the paper, you must define in terms of the TOF count or TOF ratio, what you mean by recovery period and recovery index.

**Response:** Yes. Thank you so much for your good suggestion. It is our negligent that we forgot to state the definition of recovery index in Methods. We have added these
(please see page 6, line 12-14). We should apologize for the confusion of the two concepts, recovery index and recovery period. But the truth is these are the same thing (Fisher DM, et al. Anesthesiology. 1986, 65(3):286-291.). We have corrected these in our revision (please see page 2, line 17; page 3, line 24-25; page 7, line 11-12; page 8, line 1 and legend of Figure 2 in page 17). Thank you so much for your great help!

**Point 5:** it should be acknowledged that the monitoring methods used for adjusting the dose of sufentanil and propofol are very clinical and not necessarily accurate.

**Response:** Yes. We agree with your point. After your reminder, we carefully read this part again and again, we found that we should increase the scientific and professional nature of our submission. We have revised these in our revision (please see page 4, line 14-30). Thank you!

**Minor Point:** Make sure that you have put all the references in the correct format for the journal you have submitted your manuscript to, and that the format is consistent.

**Response:** Yes. We totally agree. We have revised all the references in the correct format for *BMC Anesthesiology* (please see page 11-13). Thank you!

**Reviewer 2#**

**Reviewer's report**

**Title:** Consumption of Cisatracurium, Sufentanil and Propofol in different age groups, using a closed loop computer control system.

**Version:** 1 **Date:** 25 June 2013

**Reviewer:** Jean-marie Conil

**Reviewer's report:**

This work requires major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'

The aim of this study was to quantify the effect of age on Consumption of Cisatracurium and on neuromuscular recovery function using a computer control closed loop infusion system.
Then the authors investigated further this effect on the consumption of sufentanil and propofol. The study design is questionable. These are my specific comments:

1) Major comments:

The title “Consumption of Cisatracurium, Sufentanil and Propofol in different age groups, using a closed loop computer control system” is not appropriate. Indeed consumption of Cisatracurium uses a closed loop computer control system but it's not the case of the other drugs (Sufentanil and Propofol). The rate of Propofol infusion was adjusted according to the BIS value and the Sufentanil was given to the variations of pulse and blood pressure.

At the end of the introduction, the objective of this prospective study is not clearly defined.

In paragraph material and Methods: The three groups include different age classes. What are the criteria that permitted you to determine this age repartition? Was the age limit in each group determined a posteriori or a priori?

In the abstract the authors indicate that the dose of propofol was adjusted to a value of BIS between 40 and 60. In Materials and methods the BIS values are between 45 and 55 [“Propofol infusion was used for all patients for the maintenance of anesthesia intraoperatively. The rate of infusion was adjusted according to the BIS value (45-55)”.]

The authors write “After which the TOF monitoring was observed, and reversal agents, Neostigmine 0.35-0.50 µg/kg [8] with 0.5 mg of Atropine, were given only when at least two twitches were present according to TOF monitoring. The reference 8 corresponds to the work of Schaller offering dose of neostigmine, 34 µg/kg (to reverse a rocuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.5.)

In the "Statistical Analysis" section on which hypothesis (difference threshold) have you evaluated the size of the samples?

I propose: “The calculation of the number needed to find a difference of … % with an alpha risk of 5% and a power (1-beta) of 80% shows that … patients are needed in each group.”

Statistical methodology does not determine the best tool to detect the relationship between cisatracurium consumption and age.

In results section:

The study of the linear relationship between the dose of cisatracurium and age could clearly show the decrease in consumption of relaxant when the age increases. In all the figures the actual value of p must be given (instead of p <0.05): a p-value equal to 0.049 has not the same meaning as a value of p <0.0001.

In Table 1, the value of p comparing the three groups should be given. It might be useful to give the parameters characterizing the renal and hepatic function.

Group 2 includes 33 patients of 74 ie 44.6% of the study population. Patients aged over 65 represent 27% of patients in the study. This uneven distribution of patients in each group can be a problem in the results’ interpretation.

There is no difference for the cisatracurium between groups 1 and 2 (same remark for the sufentanil). This result raises the question of the definition of these groups with
respect to the age.

**In Discussion section**

In this work it is not shown that the Kreuer has a linear relationship to the consumption of drugs with age

From changes in age-related physiological functions, do not forget to mention the loss of lean body mass and muscle mass in particular.

The conclusion must be more nuanced

**Minor comments:**

In Discussion section: Line 8: “two groups to better better appreciate the linear regression of consumption of…” better is mentioned 2 times”…..

**Point 1: The title** “Consumption of Cisatracurium, Sufentanil and Propofol in different age groups, using a closed loop computer control system” is not appropriate.

Indeed consumption of Cisatracurium uses a closed loop computer control system but it’s not the case of the other drugs (Sufentanil and Propofol). The rate of Propofol infusion was adjusted according to the BIS value and the Sufentanil was given to the variations of pulse and blood pressure.

At the end of the introduction, the objective of this prospective study is not clearly defined.

**Response:**

1. **For the title:** Yes. We totally agree. It is our negligent. We have rewritten the title in our revision. The new title is: **Consumption of Cisatracurium in different age groups, using a closed loop computer controlled system (please see title page, line 2-3).** Do you think the current title is suitable for the paper? If you feel it is still inappropriate, please no hesitate to tell us. We will correct it to make it more scientific. Thank you so much for your good suggestion.

2. **for the Induction:** Yes. Thank you so much for your careful consideration. We have revised this part as per your suggestion (please see page 3, line 26-28).

**Point 2: In paragraph material and Methods:** The three groups include different age classes. What are the criteria that permitted you to determine this age repartition? Was the age limit in each group determined a posteriori or a priori?

In the abstract the authors indicate that the dose of propofol was adjusted to a value of
BIS between 40 and 60. In Materials and methods the BIS values are between 45 and 55 [“Propofol infusion was used for all patients for the maintenance of anesthesia intraoperatively. The rate of infusion was adjusted according to the BIS value (45-55).”].

The authors write “After which the TOF monitoring was observed, and reversal agents, Neostigmine 0.35-0.50 µg/kg [8] with 0.5 mg of Atropine, were given only when at least two twitches were present according to TOF monitoring. The reference 8 corresponds to the work of Schaller offering dose of neostigmine, 34 µg/kg (to reverse a rocuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.5.).

Response:

In paragraph material and Methods: we divided patients into three groups, those are young (20-45 yr), middle-aged (46-64 yr) and elder (> 65 yr) people. There are two reasons we divided as such repartition: First, the age of 60 or 65, roughly equivalent to retirement ages in most developed countries, is said to be the beginning of old age (From the government website of WHO http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html). Therefore, we treated age > 65 yr as older patients (Martin Briner, Erik Erickson page, 1999, on Briner's site about learning theories, USMA Department of Mathematical Sciences, Center for Assessment and Program Evaluation (CAPE), United States Military Academy at West Point). Second, we also found the criteria of age repartition from the other published papers. They described older patients as 65 yr in their articles (Mary A, et al. Front Psychol. 2013, 4: 750; Liu J. J Geriatr Cardiol. 2013, 10(3): 267-271; Finsterwald M, et al. Osteoporos Int. 2013 [Epub ahead of print]). Erik Erickson, noted developmental psychologist, described the period of young adulthood as being from age 20-45, and the task of the stage to be “intimacy vs. isolation.” (Rosel N. Int J Aging Hum Dev. 1988, 27(1): 11-23). The middle adulthood defined as 45-65 according to this stage of development stated in the following articles (Said A, et al. WMJ. 2003, 102(8): 47-51; Eberhard J, et al. J Clin Periodontol. 2013 Oct 17. doi: 10.1111/jcpe.12183. [Epub ahead of print]). So we
divided patients into three groups in our paper, these are young (20-45 yr), middle-aged (46-64 yr) and elder (> 65 yr) people. And the age limit in each group was determined a priori.

For the conflict of BIS value, we carefully revised it according to your good suggestion. Please see (page 2, line 10; page 4, line 19 and page 5, line 31). Thank you!

For the dose of neostigmine, it is our clerical error that we wrote the dose of neostigmine in the wrong manner. We have totally corrected it (please see page 6, line 6-7). For the reference of Dr. Schaller et al., they used the dose of neostigmine at 5, 8, 15, 25, or 40 μg/kg to reverse a TOF ratio of 0.5 to 0.9, that is the rocuronium-induced shallow residual neuromuscular block. They found that neostigmine, 34 μg/kg, effectively reverse a rocuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.5. In our submission, we used neostigmine to reverse neuromuscular block at reappearance of T2. Therefore, the dose of neostigmine used in our paper is 40 μg/kg actually (Adamus M, et al. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2006, 150(2):333-338). We also used the proper reference in our revision (please see reference 10). Thank you so much for your great suggestion. Without your consideration, we would not find the big mistake we have made. We really appreciate all the help you gave us!

**Point 3: In the "Statistical Analysis" section on which hypothesis (difference threshold) have you evaluated the size of the samples?**

I propose: “The calculation of the number needed to find a difference of … % with an alpha risk of 5% and a power (1-beta) of 80% shows that …patients are needed in each group.”

Statistical methodology does not determine the best tool to detect the relationship between cisatracurium consumption and age.

**Response:**

We revised this description according to your comment (page 6, lines 28-31). This information made the paper more convincing. Thank you for your good suggestion.
For the relationship between cisatracurium consumption and age: Thank you for pointing out this very important issue. We agree it is very important to evaluate the relationship between cisatracurium and age using a linear regression analysis. We added the results of the linear regression analysis in the revised version (please see page 6, line 4-5; page 7, line 23-25).

**Point 4: In results section:** The study of the linear relationship between the dose of cisatracurium and age could clearly show the decrease in consumption of relaxant when the age increases. In all the figures the actual value of p must be given (instead of p <0.05): a p-value equal to 0.049 has not the same meaning as a value of p <0.0001.

In Table 1, the value of p comparing the three groups should be given. It might be useful to give the parameters characterizing the renal and hepatic function.

Group 2 includes 33 patients of 74 ie 44.6% of the study population. Patients aged over 65 represent 27% of patients in the study. This uneven distribution of patients in each group can be a problem in the results’ interpretation.

**Response:**

Thank you for pointing out this very important issue. We agree it is very important to evaluate the relationship between cisatracurium and age using a linear regression analysis. We added the results of the linear regression analysis in the revised version (please see page 6, line 4-5; page 7, line 23-25).

For the p value of the figures: thank you! We have added the p value (please see Figure 1-4).

In Table 1, we have added the p value for all parameters (please see table 1). Thank you!

Yes, we totally agree. We have added the parameters characterizing the renal and hepatic function in the exclusion criteria of patients (please see page 4, line 10-13).

For group 2 includes 33 patients of 74 ie 44.6% of the study population and patients aged over 65 represent 27% of patients in the study: Yes. Thank you so much for your reminder. As per your suggestion, we randomly selected 20 patients from group 2 and
reanalyzed the statistical results, all these procedures repeated for three times. We still found the same results as compared with the previous one. We have stated these in our revision (please see page 7, line 26-28). Thank you so much for your careful consideration.

**Point 5: In Discussion section**

In this work it is not shown that the Kreuer has a linear relationship to the consumption of drugs with age.

From changes in age-related physiological functions, do not forget to mention the loss of lean body mass and muscle mass in particular.

The conclusion must be more nuanced

**Response:** Thank you for pointing out this very important issue. We agree it is very important to evaluate the relationship between cisatracurium and age using a linear regression analysis. We added the results of the linear regression analysis in the revised version (please see page 6, line 4-5; page 7, line 23-25).

For the age-related physiological changes in the elder patients, we have added such information in our revision (please see page 8, line 17). Thank you!

For the conclusion, we really appreciate your kind help. We have rewritten this part to make it more nuanced (please see page 10, line 9-16). Thank you!

**Reviewer 3#**

**Reviewer's report:**

This is a prospective study and the main hypothesis the authors are testing is that cis-atracurium requirement decreases with age. Cis-atracurium dosing is done using a closed-loop that is using an objective method to assess the degree of neuromuscular blockade. Overall, it is an important question and methods seem valid. However, there are several important issues that should be addressed before the manuscript can move forward.

1. **First and foremost,** there are many grammatical errors as well as problems with the choice of words. Some of these are to the point of misleading. For instance, the first sentence of the abstract reads "We devised this study to quantify the effect of age on cisatracurium in patients under general anaesthesia, using a computer control closed loop infusion system of cisatracurium." From this sentence, "the effect of age on cis-a-tracurium" can be understood in many
different meanings, including the age of the medication itself (i.e. related to its
date of production), or the effect of the patient's age on cis-atracerium
metabolism, both of which are wrong. Therefore, this sentence should be revised
to clarify the meaning. This is only the first sentence of the abstract, and there are
many other problems throughout the text with omitted words, badly constructed
sentences, superfluous language, etc. I recommend a thorough revision of the
writing of the manuscript.

2. **Second**, the title of the manuscript is misleading and not accurate. "Consumption
of Cisatracurium, Sufentanil and Propofol in different age groups, using a closed
loop computer control system" has the connotation that all 3 drugs are delivered
using a closed loop control system where, in fact, only cis-atracerium was done
so.

3. **Third**, I have some questions about methods: inclusion/exclusion criteria are
vague. How was the group allocation done? From the unequal number of patients
in 3 groups, it looks like the group assignments were done after all the patients
were enrolled. It is also mentioned that male/female ratio was kept more or less
the same. What does "more or less" mean? What procedures were followed
during enrollment to keep this gender balance? Again, looks like there was no
control, but it happened to be almost equal by chance. This is OK, but methods
make it sound like there was an effort/intervention to do this.

4. As far as exclusion criteria go, it should be specified what "significant" means for
renal, hepatic, etc dysfunction (ie creatinine >2, albumin < 3, etc)

5. Management of intraop vital signs is confusing to say the least. For hypotension,
nitroglycerin or urapidil was used: which one and how much? Did any patient end
up receiving these? For tachycardia and hypertension, sufentanil 10 to 20 mcg
was given. Again, which one of these doses (10 or 20)? What if BP did not
respond? Was sufentanil repeated? After how much time? What was the atropine
dose given? Also for respiratory management, there is some vagueness. For
instance RR was kept 12-13 breaths per minute, which of these? 12 or 13? Was it
really specified in the protocol or was it left to anesthesiologist's discretion? Also,
ABG was checked to adjust resp parameters "accordingly"... According to what?
to a pCO2 of 40? 35?

6. Most importantly, explanation of the closed-loop computer controlled infusion
also requires improvement. First of all, there is a lot of superfluous language such as
"This infusion system has the advantage for the operator..." or "This
accelerometry of the TOF ratios in the adductor pollicis muscle was proven to be
a more useful objective monitoring technique evaluating muscle relaxation or
PORC than the subjective visual/tactile assessment methods". Methods is not a
place to "sell" your methods: if you want to justify your methods by pointing out
their strengths, please do so in the discussion. Therefore, methods should be
revised to clean methods from such remarks or sentences. As for an explanation
of the system, I could not see any reference as to the details of the TOF monitor:
the technique it utilizes (accelerometry? mechano-sensor? etc), manufacturer info,
etc. Also, you mention dosing according to a percentage of T1 amplitude but you
do not clarify what the baseline was (e.g. is it 1% of the pre-induction baseline T1 amplitude? Sounds like it but it is not specified for sure). It is also strange that you measure TOF ratio and d/c patient from OR with TOF ratio >90%, but use subjective and inferior clinical criteria (e.g. head lift, hand grip) to decide extubation. Why did you do this???

7. Last but not least, you mention titrating propofol infusion to a BIS range of 40-60, but do not show the BIS data that was achieved in the end. What if group 3 had a average BIS of 59 and group 1 had an average BIS of 41? It is a big range and one can expect propofol requirements to differ unless you show me that the groups were not different in their BIS achieved.

8. For the sample size analysis, it is mentioned that a "pilot study" was used to calculate this. Can you share a little bit more about the numbers found in the pilot study (if it is unpublished) or reference the pilot study (if published).

I will not go over the results and discussion at this point: once the concerns about the methods and language/grammar is addressed, I would be happy to review the manuscript again focusing on these sections.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

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**Point 1: First and foremost,** there are many grammatical errors as well as problems with the choice of words. Some of these are to the point of misleading. For instance, the first sentence of the abstract reads "We devised this study to quantify the effect of age on cisatracurium in patients under general anaesthesia, using a computer control closed loop infusion system of cisatracurium." From this sentence, "the effect of age on cis-a-tracurium" can be understood in many different meanings, including the age of the medication itself (i.e. related to its date of production), or the effect of the patient's age on cis-a-tracurium metabolism, both of which are wrong. Therefore, this sentence should be revised to clarify the meaning. This is only the first sentence of the abstract, and there are many other problems throughout the text with omitted words, badly constructed sentences, superfluous language, etc. I recommend a thorough revision of the writing of the manuscript.

**Response:** Thank you so much for your careful consideration. As per your suggestion, we revised the first sentence of abstract (please see page 2, line 2-4), we also make a thorough revision of our submission (please see the revised submission). Thank you!
Point 2: Second, the title of the manuscript is misleading and not accurate. "Consumption of Cisatracurium, Sufentanil and Propofol in different age groups, using a closed loop computer control system" has the connotation that all 3 drugs are delivered using a closed loop control system where, in fact, only cis-atracurium was done so.

Response: Yes. We totally agree. It is our negligent. We have rewritten the title in our revision. The new title is: Consumption of Cisatracurium in different age groups, using a closed loop computer controlled system (please see title page, line 2-3).

Do you think the current title is suitable for the paper? If you feel it is still inappropriate, please no hesitate to tell us. We will correct it to make it more scientific.

Thank you so much for your good suggestion.

Point 3: Third, I have some questions about methods: inclusion/exclusion criteria are vague. How was the group allocation done? From the unequal number of patients in 3 groups, it looks like the group assignments were done after all the patients were enrolled. It is also mentioned that male/female ratio was kept more or less the same. What does "more or less" mean? What procedures were followed during enrollment to keep this gender balance? Again, looks like there was no control, but it happened to be almost equal by chance. This is OK, but methods make it sound like there was an effort/intervention to do this.

Response:

For the inclusion/exclusion criteria: Thank you so much for your reminder. We have carefully revised this part (please see page 4, line 10-13).

For the grouping method of our study: Yes, as you mentioned, the group assignments were done after all the patients were enrolled. We kept the ratio of male/female as 2/1, and there is no significant gender difference between the three groups. It is really our negligent that our vague statement will mislead the readers. Thank you so much for your good suggestion, we have revised this part in our revision (please see page 4, line 3-8 and page 7, line 4-5).
Point 4: As far as exclusion criteria go, it should be specified what "significant" means for renal, hepatic, etc dysfunction (ie creatinine >2, albumin < 3, etc)

Response: Thank you so much for your reminder. We have added the parameters characterizing the renal and hepatic function in the exclusion criteria of patients (please see page 4, line 10-13). The impairment of renal or hepatic function which could disturb the neuromuscular block agent effect.

Point 5: Management of intraop vital signs is confusing to say the least. For hypotension, nitroglycerin or urapidil was used: which one and how much? Did any patient end up receiving these? For tachycardia and hypertension, sufentanil 10 to 20 mcg was given. Again, which one of these doses (10 or 20)? What if BP did not respond? Was sufentanil repeated? After how much time? What was the atropine dose given? Also for respiratory management, there is some vagueness. For instance RR was kept 12-13 breaths per minute, which of these? 12 or 13? Was it really specified in the protocol or was it left to anesthesiologist's discretion? Also, ABG was checked to adjust resp parameters "accordingly"... According to what? to a pCO2 of 40? 35?

Response: Yes. We agree with your point that the monitoring methods used for adjusting the dose of sufentanil and propofol are very clinical and not necessarily accurate. After your reminder, we carefully read this part again and again, we found that we should increase the scientific and specific nature of our submission. We have revised these in our revision (please see page 4, line 14-30). Thank you!

Point 6: Most importantly, explanation of the closed-loop computer controlled infusion also requires improvement. First of all, there is a lot of superfluous language such as "This infusion system has the advantage for the operator..." or "This accelerometry of the TOF ratios in the adductor pollicis muscle was proven to be a more useful objective monitoring technique evaluating muscle relaxation or PORC than the subjective visual/tactile assessment methods". Methods is not a place to "sell" your methods: if you want to justify your methods by pointing out their strengths, please do so in the discussion. Therefore, methods should be revised to clean methods.
from such remarks or sentences. As for an explanation of the system, I could not see any reference as to the details of the TOF monitor: the technique it utilizes (accelerometry? mechano-sensor? etc), manufacturer info, etc. Also, you mention dosing according to a percentage of T1 amplitude but you do not clarify what the baseline was (e.g. is it 1% of the pre-induction baseline T1 amplitude? Sounds like it but it is not specified for sure). It is also strange that you measure TOF ratio and d/c patient from OR with TOF ratio >90%, but use subjective and inferior clinical criteria (e.g. head lift, hand grip) to decide extubation. Why did you do this???

Response: Thank you for your good suggestion. Yes. We should revised our language and make it more scientific and professional. We have carefully revised this part in Methods (please see page4, line 1; page 5, line 1-29).

For the extubation criteria we mentioned in our manuscript: Thank you so much for your reminder. Yes. We totally agree. It is not necessary to add the so complex criteria of extubation in Method. We have carefully revised it (please see page 6, line 8-9). Thank you!

Point 7: Last but not least, you mention titrating propofol infusion to a BIS range of 40-60, but do not show the BIS data that was achieved in the end. What if group 3 had a average BIS of 59 and group 1 had an average BIS of 41? It is a big range and one can expect propofol requirements to differ unless you show me that the groups were not different in their BIS achieved.

Response: Yes. Thank you so much for your reminder. It is really our negligent that we forgot to state the exact BIS value of each group. Although previous studies showed that A BIS between 40 and 60 is associated with moderate hypnotic state of anesthesia (Johansen JW. Best Pract Res Clin Anaesthesiol. 2006, 20(1):81-99.), it is still necessary to mentioned the BIS values of the three groups. We have added this parameter to table 1 (please see table 1). Thank you!
**Point 8:** For the sample size analysis, it is mentioned that a "pilot study" was used to calculate this. Can you share a little bit more about the numbers found in the pilot study (if it is unpublished) or reference the pilot study (if published).

**Response:** Thank you. We revised this description according to your comment (page 6, lines 28-31). This information made the paper more convincing. Thank you for your good suggestion.