Author's response to reviews

Title: Effects of continuous infusion of etomidate at various dose rates on adrenal function in dogs

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Author's response to reviews:

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Effects of continuous infusion of different etomidate doses on adrenal function in dogs
Bangyong Qin, Hongzhuan Hu, Baofeng Cao and Zhaoqiong Zhu
BMC Anesthesiology

Dear Prof. Marielette Costoy,
Thank you very much for your email with comments from the reviewers. According to these comments, the manuscript has been carefully checked and revised, and we hope that the improved manuscript can be reconsidered in the journal.

Many thanks for your continued attention.

With best regards,

Yours sincerely,

Bangyong Qin

Reply to the reviewers’ comments
Reviewer 1
General comments:
The authors have made most of the requested changes, but several more minor changes are needed prior to publication

Reply: Firstly, thank you very much for your careful review, positive comment and kind suggestion! According to your suggestion, the manuscript has been completely checked and revised, and we hope that the improved manuscript can be accepted in the journal. Thanks!

Major Compulsory Revisions:
Comments 1. The statement that ACTH stimulation was not performed because this is not routine in patients makes no sense. This is an animal experiment presumably designed to assess adrenocortical function, so the choice and use of an inferior test should be discussed. Gold-standard adrenal function testing involves ACTH stimulation to assess inducible cortisol production. Without ACTH, the decreased serum cortisol and aldosterone values reported in this paper are presumably due to diminished non-stimulated synthesis coupled with clearance (either metabolic or excretory) of hormones that were present. The authors should therefore research the literature and inform readers of the half-life of these hormones in dogs. Are the rates of disappearance consistent with total or only partial inhibition of synthesis?

Reply: According to your comments, we have added the related content in the revised manuscript as below: "Indeed, the half-life of serum cortisol, serum aldosterone and ACTH in human blood is 70 min [16], 20 min [17], and 10 minutes [18], respectively." The rates of disappearance consistent with total or only partial inhibition of synthesis have some differences. The total is higher than only partial. Thanks!

The updated reference:


Comments 2. The statement that experiments were carried "out under isothermal conditions" is confusing and not informative. The temperature of the environment where the experiments were performed must be reported. If the animals' temperatures were recorded, the authors must report the values. If they were not recorded, please state this fact in methods and in your discussion you must note that altered temperature may have affected the results.

Reply: The temperature of the Laboratory is 23#, and the animals' temperature is 37-38#. The relevant content has been added in the revised manuscript: "The temperature of the controlled laboratory was 23# and the animals' temperature was 37-38#... Meanwhile, experiments were carried out under isothermal conditions which did not affect the results. Although the altered temperature may affect the depth of anesthesia, we carefully monitored the temperature of dogs during the experiment." Thanks!

Comments 3. Please give references for the "clinical dose range" that you used as a basis for dosing in dogs. Was there an allometric adjustment for animal size? If not, you should discuss the fact that dogs may require different weight-based doses of anesthetic than humans.
Reply: Dog doses equivalent to the human 1.88 times. According to your kind suggestion, the relevant content has been revised: "We designed our experiments which references for the clinical dose range 10-20µg/kg·min⁻¹ of etomidate and dog doses equivalent to the human 1.88 times [21]." Thanks!

The updated reference:


Comments 4. You must include in the Methods the manufacturers of the radioimmunoassays that were used for various hormone levels.

Reply: The manufacturer is GC-2010 # Radio immunity counter, University of Science and Technology of China science and Technology Industrial Corporation. According to your kind suggestion, the relevant content has been revised: "The manufacturer is GC-2010#Radio immunity counter, University of Science and Technology of China science and Technology Industrial Corporation." Thanks!

Comments 5. You must report whether errors in Table 1 are sd or sem

Reply: Table 1 is presented sd, and the relevant content has been presented in the Table legend: "(n=6, ±s)". Thanks!

Comments 6. Figure one should display errors as well as mean values.

Reply: According to your kind suggestion, standard errors have been added in the Figure 1. Many thanks for your continued attention again!

The updated Figure 1:

Reviewer 2

Comments 1. The purpose of the study was to evaluate the effects of continuous infusion of various doses of etomidate on adrenal function in dogs. The authors did not state a hypothesis.

Reply: The hypothesis has been added in the revised manuscript according to your kind suggestion: "Therefore, applications and disadvantages of etomidate relying on disputed, especially whether they have a significant effect on adrenal function. Our research aims to provide reference for clinical application.” Thanks!

Comments 2. General – throughout the manuscript some of your text is red and some is black

Reply: We are very sorry because of the highlighted text. Indeed, the red text is revised content, and the black text is the original text. The highlighted revised contents can give editor and reviewers more clear revision. Thanks!

Background

Comments 3. Lines 2-3: delete “requiring mechanical ventilation.”

Reply: According to your kind suggestion, the “requiring mechanical ventilation.”
has been removed from the revised manuscript. Thanks!

Comments 4. Line 7: Change “during intubation” to “following administration.”
Reply: According to your kind suggestion, the relevant content has been revised: “following administration”. Thanks!

Comments 5. Line 12: Reference the statement about reversible inhibition of 11-beta-hydroxylase
Reply: According to your kind suggestion, the relevant reference has been provided: “reversible inhibition of the 11-beta-hydroxylase enzyme [3].”.

Reply: The hypothesis has been added in the revised manuscript according to your kind suggestion: “Therefore, applications and disadvantages of etomidate relying on disputed, especially whether they have a significant effect on adrenal function. Our research aims to provide reference for clinical application.” Thanks!

Materials and methods: animals and groups
Comments 7. Line 6 and 7: Why was anesthesia induced with sodium pentobarbital?
Reply: Indeed, sodium pentobarbital is good and cheap. The dog is mongrel dog. Dog doses equivalent to the human 1.88 times, the choice of infusion dose was a sedative dose which mainly based on the dose range of clinical applications, but beyond this range was chosen to observe for the purpose of clinical reference.

Comments 8. Line 3: What breed?
Reply: According to your kind suggestion, the "breed" indicates "mongrel", and the relevant content has been revised: "male mongrel dogs". Thanks!

Comments 9. Line 9: How were these doses chosen?
Reply: According to your kind suggestion, the relevant contents have been revised: "We designed our experiments which references for the clinical dose range 10-20µg•kg-1•min-1 of etomidate and dog doses equivalent to the human 1.88 times [17]." Thanks!
The updated reference:

Materials and methods: medicines and instruments
Comments 10. Line 2: Why did you administer vecuronium?
Reply: Vecuronium is little Influence and cheap. No histamine release and little effect on hemodynamics. According to your kind suggestion, the relevant content has been revised: "(it is no histamine release and little effect on hemodynamics and cheap [23])". Thanks!
The updated reference:
Materials and methods: anesthetic methods

Comments 11. Throughout: Your units are sometimes listed as mg/kg and others at mcg kg-1 min-1. Be consistent.
Reply: According to your kind suggestion, the relevant units have been revised: “25000 µg/kg…500 µg/kg…. 4.66-5.99 kPa….. 50 µg/kg”. Thanks!

Comments 12. Line 5: Line 8: How did you choose a BIS range of 40-60?
Reply: According to your kind suggestion, the relevant units have been revised: “(it is depth of anesthesia and close clinical anesthesia state)”. Thanks!

Comments 13. Line 13: I believe kPa is the standard for this journal.
Reply: Thank you very much for your kind suggestion. The relevant content has been revised: “4.66-5.99 kPa”. Thanks!

Comments 14. Line 15: How did you determine when vecuronium would be given? Why wasn’t this standardized? Any concerns about the potential for vecuronium affecting BIS?
Reply: Based on our preliminary experiments and the literatures, we determined the when vecuronium would be given. According to your kind suggestion, we have edited the description about it in the revised manuscript: "Subsequently intermittent boluses of vecuronium bromide (50 µg/kg) were administered for neuromuscular blockade to maintain the muscle relaxant." Thanks!

Comments 15. Line 15: Did you monitor and maintain temperature in these dogs? Concerns about temperature affecting BIS?
Reply: The temperature of the Laboratory is 23#. We monitored and maintain temperature in these dogs (37-38#), while heart rate and blood pressure relatively stable. According to your kind suggestion, the relevant content has been added in the revised manuscript: "The temperature of the controlled laboratory was 23# and the animals' temperature was 37-38#." Thanks!

Materials and methods: Observation Indexes

Comments 16. Please reference the method validation for the concentrations of cortisol, aldosterone, adrenaline, and noradrenaline.
Reply: We used radioimmunoassay method, and the relevant reference has been added in the revised manuscript: "adrenaline, and noradrenaline concentrations [24]." Thanks!

The updated reference:

Discussion
Comments 17. Line 4: Please reference this for the therapeutic index in dogs.
Reply: According to your kind suggestion, the relevant reference has been added in the revised manuscript: "therapeutic index for single bolus administration [4,25]" Thanks!
The updated reference:

Comments 18. Line 6: Please reference the statement regarding etomidate side effects.
Reply: According to your kind suggestion, the relevant contents have been revised: "We designed our experiments which references for the clinical dose range 10-20µg•kg-1•min-1 of etomidate and dog doses equivalent to the human 1.88 times [17]." Thanks!
The updated reference:

Comments 19. Line 30: Results in faster recovery compared with what?
Reply: We have checked and confirmed that the faster recovery compared with the propofol-remifentanil sedation in the experiment in reference [28], and we have revised it as below: "Etomidate, used as a continuous infusion at 10-30 µg•kg-1•min-1 for colonoscopy can maintain a good depth of anesthesia and results in faster recovery than propofol-remifentanil sedation [28]." Thanks!

References
Comments 20. I don’t believe your references are appropriately formatted for the journal. No bolding, no italics.
Reply: According to your kind suggestion, the references section has been improved according to the format in the journal. Thanks!

Figures:
Comments 21. The figures are difficult to read and don’t add more information than is available in the tables.
Reply: The tables have display the details information about the experiment. According to your suggestion, we have updated the Figure 1 and added the errors in the revised manuscript. Many thanks for your continued attention again!
The updated Figure 1: