Author's response to reviews

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

Authors:

Bangyong Qin (bangyongqin@126.com)
Hongzhuan Hu (jiongzhuanhu@126.com)
Baofeng Cao (abaofengcao@yeah.net)
Zhaoqiong Zhu (zhaoqiongzhu@yeah.net)

Version: 2 Date: 1 February 2015

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MS: 5122560431489732
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:
This is a brief report of studies in dogs assessing the effects of etomidate infusions on adrenocortical function, adrenomedullary function, and hemodynamics. The structure of the study is simple, and the results clearly support the conclusion that cortisol and aldosterone production is inhibited by etomidate in a manner that depends both on time and dose. In contrast, epinephrine, norepinephrine, hemodynamic parameters, and BIS are unaffected by time and etomidate dose.

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 reconsidered in the journal. Thanks!

Major Compulsory Revisions:

Comments 1. The manuscript is mostly written in a clear style, but needs editing in some sections. The statistical approach, using one-way ANOVA is appropriate to the study design, although the separate one-variable analyses of both time (vs. baseline) and etomidate dose (vs. barbiturate control) should be combined in a two-way ANOVA, which can be done with the SPSS software. Moreover, it is not clear from the methods section whether pair-wise statistical comparisons were based on corrections for multiple comparisons. This probably was done in the software and the authors must specify which post-hoc test was used.

Reply: According to your suggestion, we have been added with statistical method which Post-hoc test was used for pair-wise comparisons: “Pair-wise comparisons underwent post hoc testing with Dunnett’s t test.” Thanks!

Comments 2. One important question on study design was why, in these unstressed dogs, were basal cortisol and aldosterone measured, instead of using ACTH stimulation tests to assess maximal adrenocortical synthetic capacity. This is the gold-standard tests for diagnosing adrenocortical suppression in humans. The authors must justify their approach and explain why ACTH stimulation was not used.

Reply: We did not do ACTH stimulation tests, mainly due to a pre-test before anesthesia in dogs was normal adrenal function, while taking into account the clinical patients with normal adrenal function is not done generally. However, this was the limitation of our experiment. We hope that you can understand it, and many thanks for your kind suggestion again!

Comments 3. Another study design question that should be addressed in the introduction is how the specific etomidate infusion doses were chosen. Are these doses sedative or do they produce anesthesia when delivered alone (without pentobarbital)?

Reply: 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. Thanks!

Comments 4. Another important study design issue is whether core temperature was monitored and controlled during these studies. Even modest drops in temperature might affect both pharmacodynamic properties and drug metabolism.

Reply: We chose the lab at the same temperature to carry out under isothermal conditions, and this will closer to clinical practice situation. Thanks!

Comments 5. Line 107: If the reported range of PETCO2 is correct, this does not indicate controlled ventilation. The authors should change the text to “PETC02 ranged from 35 to 45 mmHg”. Ideally, they would report pH for each animal as
well. They should have monitored temperature and maintained it near 37 °C. Was this done or not?

Reply: PETC02 ranged from 35 to 45 mmHg during the experiment. We did this study because there is no fever before anesthesia on dogs, while heart rate and blood pressure relatively stable. According to your suggestion, the relevant content has been revised: "...oxygen flow rate, 2 L/min; and PETCO2, 35-45 mmHg." Thanks!

Comments 6. A surprising result, which is not discussed, is the observation that different etomidate doses do not produce different BIS values in the study animals. Given that all animals were also initially anesthetized with pentobarbital, one might conclude that etomidate has no effect on BIS values at all, although there is clearly evidence in humans that etomidate reduces BIS, but, as reported here for dogs, BIS did not vary between human subjects receiving between 0.2 and 0.4 mg/kg etomidate (see ttp://www.ncbi.nlm.nih.gov/pubmed/12925471). The authors should discuss this unexpected finding.

Reply: BIS values were changed little on different doses of etomidate, probably with no surgery stimulation and related to the use of muscle relaxant. Thanks!

Minor Essential Revisions:
Comments 7. Line 35: Please clarify that values were “significantly lower than T0”.

Reply: According to your suggestion, the relevant content has been revised: "For example, the level was 215.40±19.51 in group E2—significantly lower than the corresponding level (246.76±16.95) in group C." Thanks!

Comments 8. Line 62: change “as induce anesthesia” to “to induce anesthesia”

Reply: According to your suggestion, the relevant content has been revised: “...to induce anaesthesia”. Thanks!

Comments 9. Line 122: Which post-hoc test was used for pair-wise comparisons?

Reply: According to your suggestion, the relevant content has been revised: “Pair-wise comparisons underwent post hoc testing with Dunnett’s t test” Thanks!

Comments 10. Line 126: Add “Results are summarized in Table 1”

Reply: According to your suggestion, the relevant content has been revised: “Results are summarized in Table 1 (Figure 1)”. Thanks!

Comments 11. Line 127: Change to “Compared to T0 values...”

Reply: According to your suggestion, the relevant content has been revised: “Compared with T0 values”. Thanks!

Comments 12. Line 130: Change to “...significantly decreased from T0 values at...”

Reply: According to your suggestion, the relevant content has been revised:
“...significantly decreased relative to T0 values at T3 in group E1 and at T1-3 in groups E2-5...” Thanks!

Comments 13. Line 138: Add “Results are summarized in Table 2”
Reply: According to your suggestion, the relevant content has been revised: “Results are summarized in Table 2 (Figure 1)” Thanks!

Comments 14. Line 142: Add “Results are summarized in Table 2”
Reply: According to your suggestion, the relevant content has been revised: “Results are summarized in Table 2 (Figure 1)” Thanks!

Comments 15. Remove lines 144-150
Reply: According to your suggestion, the relevant contents have been removed from the revised manuscript. Thanks!

Comments 16. Lines 181-182: This message conveyed by this sentence is not clear. It needs to be edited or removed.
Reply: According to your suggestion, the relevant contents have been removed from the revised manuscript. Thanks!

Discretionary Revisions:
Comments 17. Why were animals heparinized for these studies?
Reply: No coagulation after using heparin was to facilitate the collection of blood samples. Thanks!

Comments 18. Although it is not mentioned in the paper, the concern about adrenocortical suppression by etomidate focuses mostly on the duration of this action, which in septic patients is reportedly up to several days following a single bolus dose. Thus, it would strengthen the value of this report for the research and clinical communities if the authors also provided results on how rapidly cortisol and aldosterone returned to normal after etomidate infusions ended. However, if these data were not collected, it is not essential.
Reply: This was the limitation of our experiment. We will conduct further experiments according to your suggestion. Thanks!

Quality of written English: Needs some language corrections before being published
Reply: According to your suggestion, the manuscript has been completely edited and proofed by a professional English editing company (certificate of English editing has been presented here), and the detailed revisions have been highlighted in the revised manuscript. Thanks!

Reviewer 2

Major Compulsory Revisions
Comments 1. Introduction, line 57: "...etomidate may be preferred over general
anesthesia." If this comment is to remain in the introduction and not be part of the authors' opinions in the discussion, it merits some form of literature support.

Reply: According to your suggestion, we have added with the reference: "...and may be preferred over propofol for general anesthesia [5]". Thanks!

Comments 2. Line 52 introduction, the description of etomidate effects on the respiratory and circulatory systems are vague. The authors should state exactly what respiration means (gas exchange, tidal volume?) and circulation (filling pressures, systemic pressures?).

Reply: We have added with the respiration (tidal volume) and circulation (systemic pressure) according to your suggestion: "minimal influence on tidal volume and systemic pressure" Thanks!

Comments 3. Line 67 introduction: the authors offer no rationale for choosing dogs for their experimental system nor do they define what they mean by adrenal function. The authors offer no rationale or support that justifies the measurement of plasma cortisol and aldosterone as a reasonable surrogate for adrenal function. If such an argument exists, the data should be representative of the dog model being put forward in the manuscript. I consider this a major concern in the manuscript and without addressing these two issues, the broader relevance and ultimate clinical applicability of the data are quite limited.

Reply: Adrenal function was normal in our preliminary experiments in dogs a pre-test before anesthesia, so we ignored the situation that is the limitation of our experiment. Many thanks for your suggestion again!

Comments 4. Again in line 168 of the discussion the issue of how plasma cortisol and aldosterone levels reflect adrenal function is raised. There is no mention in the discussion of ACTH testing and how these two different methods of measuring adrenal function compare or contrast. Without making clear the relevance of their methodology to true adrenal function, the discussion that follows on line 170-174 is difficult if not impossible to contextualize and understand. This is a major limitation of the manuscript.

Reply: We did not do ACTH stimulation tests which mainly due to a pre-test before anesthesia in dogs were normal adrenal function, while taking into account the clinical patients with normal adrenal function is not done generally. However, this was the limitation of our experiment. We hope that you can understand it, and many thanks for your kind suggestion again!

Minor Essential Revisions

Comments 5. Lines 49 and line 51 in the introduction refer to etomidate differently. Preferred terminology is sedative-hypnotic but the authors should choose one or the other and be consistent.

Reply: We chose etomidate for sedative and revised it: " However, some studies have reported that when administered to induce anesthesia..." Thanks!

Comments 6. Line 62 Introduction does not make sense- "when administered as
induce anesthesia” and should be corrected.

Reply: According to your suggestion, the relevant contents have been revised: “when administered to induce anesthesia”. Thanks!

Comments 7. Methods section, line 74. Are all 36 dogs the same breed? The breed should also be specified.

Reply: All of the 36 dogs were the same breed. Thanks!

Comments 8. Discussion lines 178-184 are in need of a re-write. The sentences include partial words (hemp.) and some words and fragments which this reviewer does not understand.

Reply: The sentences were modified and deleted. For example, "In our study, BIS values showed minimal change with different doses of etomidate, probably because of the lack of surgical stimulation and the use of a muscle relaxant." Thanks!

Comments 9. Line 184-185. No conclusions should be drawn from this work about the dose dependent effects of etomidate on BIS because the animals are already under general anesthesia with a barbiturate. This depth of anesthesia is reflected in the BIS control column.

Reply: BIS values were changed little on different doses of etomidate, probably with no surgery stimulation and related to the use of muscle relaxant. We have been revised it: "We did not perform ACTH stimulation tests in this experiment, mainly because pre-anesthetic testing in the study dogs revealed normal adrenal function. However, this is a limitation of our experiment." Thanks!

Comments 10. Lines 189-191 of Discussion. The statement that this particular infusing dose of etomidate is safe for infusion needs additional specificity. Do the authors mean all patients undergoing GA of any duration, or just short duration procedures? How do they reconcile these data with the fact that etomidate can suppress adrenal function long after the drug is stopped? They do not tell us if the 10mcg/kg/min dosing would be adequate in the absence of barbiturate. Finally, the authors do not compare this dose the current label for etomidate, or with prior infusion dosing regimens published in the literature prior to the mid 1980’s.

Reply: We consider that etomidate is safe for infusion just short duration procedures for 3 h. Thanks!

Discretionary Revisions

Comments 11. In the results section, the two data tables are the only data visualization offered. A single line graphic capturing the relationship between dose, duration of infusion, hemodynamics and adrenal function is easily created and would augment the reader’s understanding of the data and trends. It is suggested that the authors consider a graphic of some sort that shows table 1 data coupled with the hemodynamic data from table 2.

Reply: We have been revised it according to your suggestion. Thanks!
Updated Figure 1:

Figure 1. Changes of several indexes with different doses (10, 15, 20, 25, and 30 µg•kg-1•min-1) at different time points (T0, T1, T2 and T3).
(A) Changes of cortisol with different concentrations in different groups; (B) Changes of aldosterone with different concentrations in different groups; (C) Changes of epinephrine with different concentrations in different groups; (D) Changes of noradrenaline with different concentrations in different groups; (E) Changes of heart rate with different concentrations in different groups; (F) Changes of mean arterial pressure with different concentrations in different groups.

Level of interest: An article of importance in its field
Reply: Thank you very much for your positive comments!

Quality of written English: Needs some language corrections before being published
Reply: According to your suggestion, the manuscript has been completely edited and proofed by a professional English editing company (certificate of English editing has been presented here), and the detailed revisions have been highlighted in the revised manuscript. Thanks!