Title: Effects of intravenous infusion of lidocaine and dexmedetomidine on inhibiting cough during the tracheal extubation period after thyroid surgery

Authors:

hushenghong hushenghong (hushenghong-1@163.com)
Yuanhai Li (liyuanhai0312@163.com)
Shengbin Wang (aqslyywsb@163.com)
Siqi Xu (errtg555@163.com)
Xia Ju (alone2006@163.com)
Li Ma (aqslyymali@163.com)

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Author’s response to reviews:

Dear Savino Spadaro, M.D.:

Thank you very much for your letter and for the reviewers’ comments concerning our manuscript entitled “Effects of intravenous infusion of lidocaine and dexmedetomidine on inhibiting cough during the tracheal extubation period after thyroid surgery” (ID: BANE-D-18-00644). We would like to thank all reviewers for the careful and constructive examination of our manuscript. We hope to have appropriately addressed all of the concerns raised by the reviewers. I am uploading a revised version of our manuscript with changes marked with red, and the point-by-point replies to the Reviewers. We hope you find our manuscript suitable for publication in BMC Anesthesiology and look forward to hearing from you.

Sincerely yours,

Dr. Yuanhai Li, on behalf of the authors.

Reviewer reports:

luigi vetrugno (Reviewer 1): Overall it is a well written manuscript that seem to follow a severe methodology, and a fast recruitment: Ethics Committee - 2018-06-09, Chinese Clinical Trial
Registry - ChiCTR1800017482 - date of registration 28 August 2018 (that is in Chinese - difficult for me to understand), patients' recruitment in December and the final version of this manuscript in January 2019, and the final version of this manuscript in January 2019 and I congratulated with the authors' for that.

Reply 1: We thank the Reviewer for this error. Our study was registered in the Chinese Clinical Trial Registry (ChiCTR1800017482), it is now corrected in the revised manuscript (Line 57, page 3) and patients were enrolled from 2 August 2018 to 1 December 2018. It took us more than a month to finish the manuscript. In the revised manuscript it was corrected that 180 patients were enrolled from August 2018 to November 2018 (Line 60, page 3).

However, to be honest I will transfer my major concern to the authors as follow:

- Line 24 to 26....page 2: you said that "The reduction of complication, such as cough, delirium and hemodynamic disorder............ is a major concern for anaesthesiology" for me pain, bleeding and MACE are much important and in this kind of surgery the integrity of vocal cord movement much more.

Reply 2: We thank the Reviewer for picking up this error in the passage. Cough during tracheal extubation may lead to several complications, such as hypertension, tachycardia, myocardial ischemia and postoperative bleeding [3-5]. Furthermore, postoperative bleeding in thyroid surgery is still significant and is often associated with severe complications including cervical hematoma, reoperation and cardiac arrest. It is now corrected in the revised manuscript (Line 38 to 41, page 2). In the study, experienced surgeons preserved the anatomical integrity of motor nerves by visual identification and exposure both of the external branch of the superior laryngeal nerve and the recurrent laryngeal nerve during thyroid surgery. It is now corrected in the revised manuscript (Line 105 to107, page 5).

- Line 41 to 42 page 2: "These complications may negatively impact the quality of recovery" however there is/are no relation with the outcome.

Reply 3: We thank the Reviewer for catching this error. We have deleted “These complications may negatively impact the quality of recovery".
- Line 44 to 48 "Therefore, the inhibition of cough is considered to be more important for thyroid than any other surgical factor" so I respect your point of view but let me to disagree a little bit and to point out my major concern about nerve damage.

Reply 4: We thank the Reviewer for pointing out this important message. The recurrent laryngeal nerve was prevented injury by visual identification and intraoperative neuromonitoring during surgery. it is now corrected in the revised manuscript (Line 107 to 108, page 2).

- The grade of cough was: no cough, 1 cough, > 1 cough lasting for < 5 sec and grade 3 severe, sustained cough for > 5 seconds. It is difficult for me to correlate this time with outcome.

Reply 5: We thank the Reviewer for pointing out the misleading statement in regards to the incidence and severity of cough in the passage. The incidence and severity of cough within 5 minutes during the extubation was recorded: 0=no cough, 1=minimal (single) cough, 2=moderate (≤5s) cough and 3=severe (>5s) cough (bucking). It is now corrected in the revised manuscript (Line 115 to 116, page 6).

- statistical analysis: you said that a pilot study was performed to estimate an appropriate sample size without explain to us how you can obtain this number.

Reply 6: We thank the Reviewer for pointing out this important message. Calculation of sample size was based on the incidence of cough. In the pilot study, the two treatments infusion reduced the incidence of cough by 35%, and incidence of cough in the CON group was 62% and an α of 0.05, 55 patients would be required in each group (assuming a power of 0.80). Anticipating a study drop-out rate of 10%, we included 60 patients per group. It is now corrected in the revised manuscript (Line 126 to 129, page 6).

- Finally, are you protocol complication free? There is there are an other face of the moon.

Reply 7: We thank the Reviewer for pointing out this shortcoming. The study was demonstrated that intravenous infusions of dexmedetomidine resulted in bradycardia and delayed time to
awareness when compared with lidocaine and normal saline. It is now corrected in the revised manuscript (Line 240 to 241, page 11).

Alessandro Belletti, M.D. (Reviewer 2):

The work is potentially interesting; yet, there are some issues that in my opinion require to be addressed:

1. It is not entirely clear to me who was blinded, although I understand that this was a probably a double-blind study. The Authors should however clearly specify that patients, treating physicians and outcome assessors were blinded to group assignment, and study drug were prepared by study personnel not otherwise involved in the study. Furthermore, the method used to ensure allocation concealment should be specified: sealed opaque envelopes? Web-randomization by study personnel not otherwise involved?

Reply 1: We thank the Reviewer for pointing out this important message. In the study, subjects were randomised to LIDO group, DEX group and CON Group with a 1:1:1 allocation using computer-generated random number. Group assignments were kept in sealed envelopes, and only the nurse responsible for preparing the anesthetics was allowed to open the envelope and the assigned drug. The assigned drugs according to group assignments in syringes which has no difference in appearance. The patients, data collectors (anesthesiologist) did not know the drugs used for intravenous administration. It is now corrected in the revised manuscript (Line 69 to 74, page 4).

In the LIDO group, the patients were given an IV bolus infusion of lidocaine (2%)1.5 mg/kg made to 20ml with normal saline and 20ml normal saline respectively, over 10 minutes before induction of anesthesia, followed by a continuous IV infusion of lidocaine 1.5mg/kg made up to 20ml and 20ml normal saline every hour until 30 minutes before the end of surgery, respectively. In the DEX group, patients were given IV bolus infusion of dexmedetomidine 0.5 μg/kg made to 20ml with normal saline and 20ml normal saline respectively, over 10 minutes before induction of anesthesia, followed by a continuous IV infusion of dexmedetomidine 0.4μg/kg made up to 20ml and 20ml normal saline every hour until 30 minutes before the end of surgery, respectively. In the CON group, the patients were given an 20ml normal saline and 20ml normal saline respectively, over 10 minutes before induction of anesthesia, followed by a continuous IV infusion 20ml normal saline and 20ml normal saline every hour until 30 minutes before the end of surgery, respectively. It is now corrected in the revised manuscript (Line 81 to 92, page 4 to 5).
2. The Authors should improve their description of sample size calculation. They refer to a pilot study, by no additional data are reported. Were results of the pilot study published? Which results yielded this pilot study? Which was the expected incidence of cough in the control group and the estimated reduction in the treatment groups?

Reply 2: We thank the Reviewer for pointing out this important message. Calculation of sample size was based on the incidence of cough. In the pilot study, the two treatments infusion reduced the incidence of cough by 35%, and incidence of cough in the CON group was 62% and an α of 0.05, 55 patients would be required in each group (assuming a power of 0.80). Anticipating a study drop-out rate of 10%, we included 60 patients per group. It is now corrected in the revised manuscript (Line 126 to 129, page 6).

3. Concerning outcome, I believe that reporting only cough and drainage amount is somewhat insufficient. In my opinion, additional outcome data should be reported, and in particular:

- incidence of study-drug side effects, i.e. local anesthetic toxicity, supraventricular and ventricular arrhythmias, intraoperative bradycardia and hypotension, intraoperative need for vasopressors, intraoperative fluid balance, postoperative need for supplemental oxygen or prolonged respiratory support (e.g. NIV or reintubation), postoperative length of hospital stay, postoperative mortality, postoperative complications according to Clavien-Dindo classification.

Reply 3: We thank the Reviewer for pointing out this shortcoming in our manuscript.

In the study, incidence of study-drug side effects including local anesthetic toxicity, supraventricular and ventricular arrhythmias, intraoperative bradycardia and hypotension, intraoperative need for vasopressors and prolonged respiratory support were observed and recorded. No adverse effects including local anesthetic toxicity, supraventricular or ventricular arrhythmias, hypotension, need for vasopressors and prolonged respiratory support were observed in the study. In the DEX group, bradycardia (HR<60 beat/min) was noted in 35 patients (58.3%) without hypotension, and one patient's HR was reduced by 40 beat/min, and that was treated with atropine 0.5mg iv. No bradycardia was noted in LIDO group and CON group. No patients required prolonged respiratory support after the tracheal extubation in the three groups. It is now corrected in the revised manuscript (Results section, page 7to 8). Intraoperative fluid balance was recorded. It is now corrected in the revised manuscript (Table 1). The time to awareness and the postoperative length of hospital stay were recorded. It is now corrected in the revised manuscript (Table 5). None of the patients died after thyroid surgery in the study.
- incidence of major surgery-related adverse events potentially prevented by cough prevention, i.e. cervical hematoma, need for surgical revision, need for transfusion, days until drainage removal...

Reply 4: We thank the Reviewer for catching this shortcoming. The incidence of cervical hematoma, need for surgical revision, need for transfusion and days until drainage removal were observed and recorded. All drainages in the LIDO group and DEX group were removed within 48 hours after surgery, while 60% (36 cases) drainages in the CON group were removed. There was a 1.7% incidence of cervical hematoma and need for surgical revision without transfusion after surgery in the CON group. It is now corrected in the revised manuscript (Results section, page 7 to 8).

- if available, postoperative pain scores.

Reply 5: We thank the Reviewer's advice. Patients were assessed in surgical ward for pain intensity using a 10 cm visual analogue scale (VAS: 0 = no pain, 10= the most imaginable pain). Postoperative pain scores were recorded at any point time after surgery. It is now corrected in the revised manuscript (Table 6).

4. As a related point, the Author should discuss the clinical significance of their findings. I.e. the drainage volume was reduced by something like 25-30 mL, looking at figure 3. Do the Authors believe this is a clinically-relevant difference?

Reply 6: We thank the Reviewer for pointing out this important message. Compared with the CON group, the volume of drainage was significantly reduced in the LIDO group and the DEX group within the first and second 24 hour after surgery (P<0.05), and there was no difference in the volume of drainage between the two treatment groups. It is now corrected in the revised manuscript (Table 4).
5. I kindly ask the Authors to provide absolute data for both hemodynamic parameters and drainage amount. I appreciate the figures, yet I would also prefer to have the precise values of MAP, HR and volume, rather than trying to estimate them from the graphs.

Reply 7: We thank the Reviewer's advice. We provided absolute data for both hemodynamic parameters and drainage amount. It is now corrected in the revised manuscript (Table 3 and Table 4).

6. Given that postoperative bleeding is a key outcome of this study, I suggest to present additional data on preoperative coagulation (e.g. platelets, coagulation test, and use of antithrombotic medications), although I acknowledge that given inclusion criteria (ASA I-II 18-65 yr old subjects) it is unlikely to have included patients with coagulation abnormalities or under antithrombotic therapy.

Reply 8: We thank the Reviewer for pointing out this important message. In the study, we have improved platelets and coagulation test dates. It is now corrected in the revised manuscript (Table 1). The supplementary exclusion criteria in this study included platelet abnormality, coagulation abnormalities and anticoagulation. It is now corrected in the revised manuscript (Line 67, page 4).

7. The Authors report trial registration on Chinese Clinical Trial Registry in the Abstract, and on ClinicalTrials.gov in the Methods. Please edit for consistency.

Reply 9: We thank the Reviewer for pointing out this error in our manuscript. Trial registration: Chinese Clinical Trial Registry (ChiCTR1800017482). (1 August 2018). This study was registered in the Chinese Clinical Trial Registry (ChiCTR1800017482). It is now corrected in the revised manuscript (Line 33, page 2 and Line 57, page 3).