Author’s response to reviews

Title: Association between postoperative cough and thyroidectomy: a prospective study

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Author’s response to reviews:

Dear editors and reviewers,

Thanks for your precious comments and suggestions, we have revised this manuscript based on your comments, the revised section is in red color. Please see as below,

Reviewer #1,

Q1: In this study, the control group included patients who underwent superficial parotidectomy, submandibular gland excision, branchial cleft cyst excision, or thyroglossal duct cyst excision. However, the excision of thyroglossal duct cyst might influence the function of larynx or oropharynx because the body of hyoid bone is removed and it abuts the larynx. Also the excision of branchial cleft cyst might be related with the function of vagus nerve or pharynx because 2nd branchial cleft cyst may be in contact with the vagus nerve or pharynx. Therefore, authors need to exclude patients with thyroglossal duct cyst and branchial cleft cyst in the control group.

   Reply: Thanks for the suggestion, we have excluded patients with thyroglossal duct cyst and branchial cleft cyst in the control group, and all the statistic analyses are re-calculated. Please see the content in the abstract, paragraph 3 in methods section, paragraph 1 in results section, Table 1 and Table 2.

Q2: The LCQ was done preoperatively and at 2 weeks postoperatively. Therefore, it is not chronic cough. Authors need to modify the title of the manuscript.

   Reply: Thanks for the comments, we have revised the title into “Association between postoperative cough and thyroidectomy: a prospective study”.

Q3: The postoperative cough can be caused by the laryngitis or laryngeal trauma related with the orotracheal intubation. Therefore, it may be necessary to examine the larynx using flexible laryngoscopy after operation in the control and case groups.

Reply: Thanks for the comments. We can not agree with you any more, but we do not routinely examine the larynx using flexible laryngoscopy for patients with cough, this may bring some bias during our analysis, we have added the limitation discussion content. Please see line 1-6 in the last paragraph in Discussion section.

Q4: Actually, the exact cause of cough after thyroidectomy is not determined yet. Therefore, authors do not speculate the causes of cough in the Discussion.

Reply: Thanks for the suggestions. In our view, the most likely cause of this was associated with the branches of the recurrent laryngeal nerve. Small branches of the nerve, such as the tracheal branch, are often encountered during thyroidectomy, and could inadvertently be resected during central neck lymph node dissection. However, the actual frequency of branch excision has not been clearly documented. Therefore, we cannot clarify whether the branch excision is associated with postoperative cough. Another potential explanation was the tracheal thermal damage associated with the usage of high-frequency electric surgical knives and ultrasonic scalpel during operation. We have added the content in the text, please see line 6-12 in the paragraph 4 in the discussion section.

Reviewer #2,

Q1: This is an interesting study evaluating the impact of thyroid lobectomy on health-related quality of life from coughing 2 weeks after surgery. The authors have chosen patients who will undergo a unilateral procedure to enroll in their cohort. The control consists of those with other head-and-neck operations. It is unclear what kind of operations these are and if the neck is still being operated on.

Reply: Thanks for the comments, in experimental group, all patients underwent unilateral thyroidectomy and central node dissection, and in control group, 63 patients underwent superficial parotidectomy, and 40 underwent submandibular gland excision. Patients undergoing neck dissection, oral cavity and throat surgery were excluded, please see line 4-6 in paragraph 3 in methods section.

Q2: Perhaps a third group should be assessed including those who undergo abdominal or extremity surgery to evaluate the role of the endotracheal tube.

Reply: Thanks for the comments, a third group will surely increase the reliability of our research, but in current study, the control group is designed to shield the effect of endotracheal tube. In our future work, we will add more control groups to clarify these questions.
Q3: I am unclear as to why the authors chose 2 weeks as the final point of assessment? This seems like post-operative recovery time and would be more beneficial to follow these patients out for at least 3-6 months.

Reply: Thanks for the comments, in fact, before we conduct this research, we have noted the cough symptom of most patients have returned to normal in the second to forth week after operation. Furthermore, consistent with previous work (reference 6), and the LCQ questionnaire is used to evaluate the cough-related quality of life in the last two weeks, therefore, we chose 2 weeks as the final point of assessment. In future study, we will follow patients out for 3-6 months or longer. Moreover, we have added the limitation content, the LCQ questionnaire in current study just represented the short term adverse effect on cough of thyroidectomy, more long term clinical data was needed to clarify the question. Please see line 4-6 in the last paragraph in discussion section.

Q4: the authors should provide more details about the questionnaire that they are using. It seems that it was validated on patients with CHRONIC cough, and the authors are testing it for acute change in symptoms.

Reply: Thanks for the comments, we have added more description about the questionnaire. The LCQ questionnaire was originally developed in those with chronic cough, but its validity and responsiveness had been demonstrated in assessing acute cough or postoperative cough [6, 9, 10]. The LCQ is designed for self-administration and takes less than 5 min to complete. The questionnaire consists of 19 items and each item represents an adverse event caused by cough, a 7-point Likert scale was used for scoring the responses. These 19 items were divided into three domains that consider the physical impacts (such as effect of cough on sputum production, stomach and chest pain,), psychological impacts (such as effect of cough on embarrassment/anxiety), and social impacts (such as cough interfering with job/daily life, enjoyment of life). Three domain scores and a total score are calculated, with domain scores ranging from 1 to 7 and total scores from 3 to 21, a higher score reflects better health status [11]. Please see paragraph 4 in methods section.

Q5: What is a mean score for the general population?

Reply: Thanks for the comments, in current study, patients with chronic cough were excluded. Therefore, the preoperative mean total LCQ score was 21 in both the experimental and control groups, and there was no significant difference ($p>0.05$).

Q6: What is the clinical significance?

Reply: Thanks for the comments, one of the main significance is to provide the evidence that thyroidectomy will increase the occurrence of postoperative cough; another is to better communicate with the patient during the treatment. Please see last three lines in paragraph 1 in discussion section.
Q7: It seems that there is overlap between the two groups. Are there other risk factors that would contribute to the scores such as smoking status or presence of reflux or duration of the case?

Reply: Thanks for the comments, firstly, chronic cough is usually associated with presence of reflux, in current study, patients with chronic cough were excluded. Secondly, we have re-reviewed the patients’ medical records again, and extracted the data of smoking, and found there was no significant difference regarding smoking between the two groups, please see line 9-10 in paragraph 2, and line 4-9 in paragraph 3 in methods section.

Q8: It is unclear if a multivariable analysis was done or if the findings are a univariable analysis.

Reply: Thanks for the suggestion, a univariate analysis is performed. Please see line 3-4 in last paragraph in the methods section.

Q9: I am curious as to why the authors chose only to evaluate patients undergoing unilateral thyroid lobectomy and not total thyroidectomy?

Reply: Thanks for the comments. Before we conduct this research, our group have discussed the enrolled patients deeply. Patients with total thyroidectomy might have more serious cough than patients with unilateral thyroidectomy, although it is easier for us to find difference between the two groups, it will increase the heterogeneity in the experimental group. Therefore, only patients with unilateral thyroidectomy are enrolled.

Q10: was a sample size calculation performed? What difference were the authors intending to find and is their study adequately powered. Detailed sample size calculation needs to be provided.

Reply: Thanks for the comments, data from our pre-experiment of 30 patients undergoing unilateral thyroidectomy and central node dissection showed the mean total score was 18.0 (standard deviation: 5.2), therefore, we defined the mean total score in experimental group was 18.0 with standard deviation of 5.0. With regard to control group, no similar literature was available for studying, general anesthesia might be a little responsible for postoperative cough, and we speculated that patients would had better total scores, therefore, we defined the mean total score in control group was 20.0 with standard deviation of 5.0. Therefore, assuming a two-tailed type 1 error rate of 5%, a sample size of 198 cases in experimental and 66 cases in control group were required to give greater than 80% power to find significant difference between the two groups. Please see paragraph 5 in methods section.

Great thanks to you for your precious comments and suggestions, we have revised the manuscript based on the comments and suggestions, and also the authors of Yao Wu and Qigen Fang have made the main contribution in the revision, therefore, the author list is changed, and all the authors have approved this change, the attached file is the authorship form, we hope now this paper could be accepted for publication.
Best wishes

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