Author’s response to reviews

Title: Multimodal analgesia with ropivacaine wound infiltration and intravenous flurbiprofen axetil provides enhanced analgesic effects after radical thyroidectomy: a randomized controlled trial

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Author’s response to reviews:

Dear Dr. Cummings,

Thank you very much for your letter and advice regarding our manuscript. We are truly grateful for the comments from the reviewers. We have revised our manuscript in accordance with the reviewers’ comments and would like to re-submit it for your consideration. The amendments are indicated in the revised manuscript by highlighting. Our point-by-point responses to the reviewers’ comments are listed below.

We hope that the revised version of our manuscript is considered acceptable for publication in your journal.

We look forward to hearing from you soon.

Best wishes,

Xiaoxi Li, Ling Yu, Jiaonan Yang and Hongyu Tan
Point-by-point responses to the reviewers’ comments:

Dr. Honzhen Hu (Reviewer 1):

1. Page 2, Line 39, 1:200000, by volume or concentration?

Response: Thank you for your question. In our study, 0.5% ropivacaine was mixed with epinephrine in a ratio of 1:200,000. The concentration of epinephrine in the mixed local anesthetic was 5 μg/ml. To make this clearer, we have added this information on line 39 of page 2 and line 143 of page 8.

2. In the background, the authors stated that one of the purposes by using multimodal analgesia is to reduce the side effect of opioid consumption. However, the side effects of the combination of flurbiprofen and ropivacaine are almost the same as that by tramadol in the results. They argued that treatment with dolasetron and propofol might prevent these side effects. If this is the case, maybe they should add a few sentences in the introduction for the effectiveness of the treatment of these side effects.

Response: Thank you for your advice. Clinical research shows that postoperative nausea and vomiting (PONV) is primarily caused by the use of inhalational anesthesia and opioid analgesics. Studies have shown that the incidence of PONV is reduced by the administration of antiemetic drugs such as 5-HT3 receptor antagonists (e.g., dolasetron), as well as the use of total
intravenous anesthesia. We have added this information in the Background section of the revised manuscript (please see line 73, page 4).

3. Page 5. Line 85. It will help to add a few sentences to introduce ropivacaine immediately after the introduction of flurbiprofen at Line 85.

Response: Thank you for your helpful suggestion. Ropivacaine is currently the most popular long-acting local anesthetic, and is widely used for local anesthesia due to its reduced toxic potential in comparison with similar agents. We have added this information in the Background section of the revised manuscript (please see line 96, page 5).

4. Page 10. Line 196. The data of the mean blood pressure should be included in Table 1.

Response: Thank you for your suggestion. We have added a new table that includes the mean blood pressure data (please see line 218, page 12).

Dr. Heyn (Reviewer 2):

1. The authors used tramadol for pain management in the control group. The authors should give reasons why they choose tramadol instead of another pain killer for pain control. Since tramadol is not common for pain control in patients during recovery ward.

Response: Thank you for stating your concerns. Opioids (e.g., morphine and sufentanil) are the most commonly used type of analgesic for moderate to severe postoperative pain during recovery. Tramadol is a synthetic opioid that is widely used for mild and moderate postoperative pain. Compared with other pure opioid agonists, tramadol causes less respiratory depression and sedation. In our clinical experience, tramadol is prescribed for analgesia in patients undergoing thyroid surgery because it is effective in relieving mild to moderate pain, causes less respiratory depression and sedation than other opioids, and has a relatively low cost. After overall consideration of ethical issues and patient comfort, we chose to use tramadol for pain management in the control group instead of other opioids or a placebo. We have added this information with supporting references in the Background section (please see line 65, page 4).
2. The authors should describe in more detail why they choose ropivacaine 0.5%?

Response: Thank you for your suggestion. Ropivacaine is currently the most popular long-acting local anesthetic due to its reduced toxic potential compared with other local anesthetic agents. According to previous studies, ropivacaine provides adequate analgesia via wound infiltration at concentrations of 0.25%, 0.5%, and 0.75%. Based on the literature and our experience, we chose to use 0.5% ropivacaine for local anesthesia because this concentration provides good analgesic effects with few adverse effects. We have added a detailed description of why we chose to use 0.5% ropivacaine in the revised manuscript (line 96, page 5; line 262, page 15).

3. The authors used ropivacaine in combination with epinephrine – they should mention the problems and contraindications for the usage of epinephrine.

Response: Thank you for your suggestion. We have added the following sentence in the revised manuscript. “However, epinephrine should be applied with caution in patients with severe hypertension, or cardiovascular and cerebrovascular diseases, as it may cause tachycardia and hypertension if absorbed intravascularly” (please see line 268 on page 15).

4. Postoperative pain scores are very low in both groups (mean < 2 in both groups) which is a good result after operation. This may imply that both regimens are helpful in these patients. Furthermore, the difference of NRS 0.5 between both groups is statistically significant, but clinically irrelevant.

Response: Thank you for your critical review. Indeed, 80% of the present patients had a pain score of less than 4. The possible reasons for these low pain scores are that thyroidectomy only causes mild to moderate postoperative pain, and that the intensity of postoperative pain may vary in accordance with the surgical approach and anesthetic management. In our study, the application of a small incision (approximately 4–7 cm) in thyroidectomy may have resulted in low pain scores in both groups during the 48 h postoperative period. Our study showed that pain control after thyroid surgery can generally be accomplished with either a multimodal analgesia regimen of pre-incision wound infiltration and flurbiprofen axetil or with a single dose of tramadol, mostly without additional analgesics. However, our results showed that the average pain score reached its maximum at 2 h postoperatively in the control group (1.6 at rest and 2.6 during coughing/swallowing) and remained at a relatively high level until 8 h postoperatively.
During the 2–8 h postoperative period, the average pain scores of the control group were 1.4 at rest and 2.0 during coughing/swallowing, whereas the average pain scores of the multimodal analgesia group were 0.6 at rest and 1.2 during coughing/swallowing. The postoperative pain score in the multimodal analgesia group reached its maximum at 24 h postoperatively at rest and 8 h postoperatively during coughing/swallowing (maximum pain scores were 0.6 at rest and 1.4 during coughing/swallowing). However, the maximum postoperative pain in the multimodal analgesia group was still relatively low compared to that in the control group at the same timepoint. These results suggest that multimodal analgesia resulted in delayed occurrence of maximum postoperative pain (and a relatively low maximum pain score), and in significantly superior postoperative analgesia to tramadol during the early postoperative period (2–8 h postoperatively). This is meaningful, as several studies have indicated that the first few hours following thyroidectomy are the most crucial for pain management because patients experience maximum pain during this time period. We have added this information in the Discussion section (line 271, page 15; line 307, page 17).

5. One of the side effects of tramadol is nausea (and as a result swallowing as well). This may result in higher frequency of swallowing in the group with tramadol and may be also an explanation for the higher NRS scores during coughing/swallowing. Therefore, tramadol is not the best option in patients after thyroidectomy. The authors have to discuss this point.

Response: Thank you for your critical review. We agree that tramadol may lead to a higher frequency of swallowing, and may explain the higher pain scores during coughing/swallowing in the control group compared with the multimodal analgesia group. However, the incidence of nausea did not significantly differ between the two groups in our study, which means that the frequency of swallowing was similar in both groups. This suggests that the comparison of the two groups regarding the pain scores during coughing/swallowing would not have been affected by this adverse effect of tramadol. However, we appreciate the reviewer’s consideration and believe that the reviewer has raised a very good point. We have addressed this issue on line 294, page 16.

6. The authors suggest that their multimodal regimen is safe in patients with thyroidectomy. Since the regimen was only used in 20 patients, it is difficult to suggest that this is a safe procedure. To give such advices, more than 20 patients have to be analyzed.
Response: Thank you for your critical review. The multimodal regimen consisted of a dose of flurbiprofen axetil (within the recommended dose range) and a long-acting local anesthesia with minimal toxicity (within the recommended dose range and volume). We excluded patients with contraindications to this multimodal regimen (such as a history of allergic reaction to NSAIDs, coagulation disorders, gastrointestinal ulceration, severe hypertension, severe cardiovascular and cerebrovascular diseases, and renal dysfunction). Our results showed that the incidence of adverse effects was low. In our experience, the present multimodal regimen can be safely applied under the clinical conditions described. However, after careful consideration, we agree with the reviewer that it is not appropriate to use the word “safe”. Thus, we have reworded the manuscript to state that “our results demonstrated a low incidence of adverse effects due to multimodal analgesia with ropivacaine wound infiltration and intravenous flurbiprofen axetil (both administered within their recommended dose and volume) in patients undergoing thyroidectomy” (please see line 332 page 18); “Multimodal analgesia with ropivacaine wound infiltration and intravenous flurbiprofen axetil improves the quality of postoperative analgesia in patients undergoing radical thyroidectomy, and has few adverse effects.” (please see line 352, page 19).

7. The authors failed to figure out the novelty of their since they quote different studies which analyzed this issue before and showed a pain relief when using local anaesthesia.

Response: Several previous studies have investigated the effectiveness of using local anesthesia for postoperative pain relief. However, the results of these previous studies are controversial. Some studies reported that local anesthesia reduced postoperative pain and analgesic requirement, while other studies reported a lack of analgesic effect. Additionally, some studies demonstrated that the analgesic effect of local anesthesia was only maintained for a short period of time (within 2 h postoperatively), but did not reduce pain for more than 2 hours. We hypothesized that the use of a multimodal analgesia regimen comprising local anesthesia plus a non-steroidal anti-inflammatory drug would achieve effective analgesia for a longer postoperative period. We chose flurbiprofen axetil, which has the unique property of a high affinity for selective congregation in inflammatory tissue, and provides sustained drug release. We also added epinephrine to prolong the local anesthetic action. We expected this combined regimen to improve the quality of postoperative pain management both in the immediately postoperative period and during the whole postoperative period. Our results showed that pain control after thyroid surgery can generally be accomplished with either a multimodal analgesia regimen of pre-incision wound infiltration and flurbiprofen axetil or with a single dose of tramadol, mostly without additional analgesics. However, the multimodal regimen delayed the
occurrence of maximum postoperative pain, provided superior pain relief compared with tramadol alone (especially during the early postoperative period), and provided adequate analgesia for 48 h postoperatively (average pain scores were 0.9 at rest and 1.6 during coughing/swallowing), mostly without requirement for additional analgesics. During the early period of postoperative pain (2–8 h postoperatively), multimodal analgesia achieved good levels of patient comfort (0.6 at rest and 1.2 during coughing/swallowing); this is meaningful as previous studies have reported that the first few hours postoperatively is the most painful period for patients undergoing thyroid surgery. Thus, the multimodal regimen helped to avoid the use of opioids for postoperative pain treatment, which is beneficial for patients. We believe that this multimodal regimen is an excellent analgesic protocol for patients undergoing thyroidectomy, with few adverse effects. The present study is the first to evaluate multimodal analgesia for thyroidectomy. We have discussed this in detail in our revised manuscript. We sincerely hope that the reviewers will be satisfied with our explanation of the novelty of our study.