

## Peer Review File

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### Reviewer A

The manuscript provides clinically useful information on the dosage of cisatracurium, one of most frequently used muscle relaxant in general anesthesia, in thyroid surgery with intraoperative neuromonitoring. Good work.

### Reviewer B

Comment 1: P6 L211 “Pearson chi-squared test or Fisher’s exact test” Is Pearson true?

Reply 1: Thank you for your question. We used Pearson’s chi-squared test or Fisher’s exact test to analyze categorical variables. The appropriate method was chosen, depending on the data in the fourfold table. For example, differences in patient sex and type of thyroidectomy between the two groups were analyzed with Pearson’s chi-squared test, whereas differences in the need for assistance during intubation and hoarseness after extubation between the two groups were analyzed with Fisher’s exact test. We have consulted a statistician to ensure proper application of statistical analyses.

Comment 2: P1 L 21 The running title is too long.

Reply 2: Thank you very much for your advice. The running title has been changed to “Dosage effect of cisatracurium on IONM”, in accordance with the editorial policy (Please see page 2, line 23).

Change in the text: “Running title: Dosage effect of cisatracurium on IONM.”

### Reviewer C

I compliment the authors for this elegant study

I found it really interesting for surgeons using neuromonitoring for thyroid surgery

I have no questions

### Reviewer D

Comment 1: The major problem with this study is that it is not clear what should be novel and thus warrant publication in literature: cisatracurium has been used as neuromuscular blocking agent (NMBA) for many, many years. It has been used by clinicians for facilitation of intubation for thyroid surgery as well, during many, many years. Maybe in different doses (1, 2, 3 times the ED95) depending on the neuromuscular block management the individual clinician preferred. When one waits long enough (see: your intubation times) even with fairly low doses of whatever NMBA, more or less acceptable

intubating conditions can be reached. Depending on that dose, the time to be able to use neuromonitoring in the typically described surgical procedure will be shorter or somewhat longer. However, it could have been anticipated that with a dose of only once the ED95, intubating conditions would have been quite poor and inferior to when a dose of twice the ED95 was used: intubating conditions after once a ED95 dose are known to be not quite acceptable. You find this in the manufacturer's guidelines of the drug(s) and in the different phase trials for the different NMBAs available. It is one of the reasons why the pharmacological variable 'ED95' was invented. Although the authors have merits and did efforts to perform this study, as a reviewer, I sincerely not see what novelty in their findings should be encountered.

Reply 1: Thank you for raising your concerns. The aim of this study was to investigate the optimal dosage to provide both adequate muscle relaxation for tracheal intubation and timely IONM for thyroidectomy. Cisatracurium has indeed long been used as a neuromuscular blocking agent during anesthesia. It has excellent hemodynamic stability and its metabolization is independent of organ function. These characteristics make cisatracurium especially favorable for old and critical patients. Moreover, the recovery index of cisatracurium is slightly shorter than that of rocuronium and other nondepolarizing NMBAs (Ann Card Anaesth 2008;11(2):80-90; Eur J Anaesthesiol 2004;21(11):877-81), which may be advantageous during thyroid surgery with IONM. However, the dosage of cisatracurium for intubation is generally determined according to individual clinician's preference in this specific clinical setting. The optimal dosage of cisatracurium that not only provides adequate muscle relaxation during intubation but also allows for reliable, timely neuromonitoring interpretation, has not been investigated.

The use of NMBAs is very important for tracheal intubation. However, insufficient recovery from neuromuscular blockade may hinder IONM and prolong the surgical process. Previous studies have indicated that intubation conditions differ significantly with different dosages of rocuronium (Anesth Essays Res 2012;6(1):62-9; Cell Biochem Biophys 2015 Jan;71(1):143-6). In our study, intubation conditions (evaluated with the Cooper score) also varied significantly among different groups. However, the guidelines on IONM recommend using a dose of NMBA that is lower than the manufacturer's guidelines (for example, 1× the ED95 of rocuronium is recommended) in this clinical situation. Although standard procedures for the use of IONM have been established, some issues remain to be resolved before its routine application during anesthesia. Therefore, we believe it is of clinical importance to determine the dosage effect of cisatracurium, which is one of the most commonly used NMBAs with distinct advantages in this specific clinical situation. Successful early detection of IONM helps surgeons ensure a functional intact RLN, whereas a delay may cause anxiety for surgeons and can lengthen the duration of surgery. Therefore, determining the effective dosage of cisatracurium during IONM is clinically important for both patients and clinicians. To our knowledge,

this is the first study to evaluate the optimal dosage of cisatracurium in patients undergoing radical thyroidectomy with IONM. Some of these points were made in our original manuscript, and we have expounded in detail on the novelty of our study in the revised manuscript. We sincerely hope that our data will be helpful. (Please see page 5, line 81 and page 6, line 96 and 101).

Changes in the text: “A negative stimulation during surgery may cause anxiety for surgeons and may prolong operation time.” “Cisatracurium has long been used by clinicians to facilitate intubation for thyroid surgery. However, the dosage of cisatracurium for intubation of patients undergoing thyroid surgery with IONM has generally been determined according to the individual clinician’s preference.” “The optimal dosage of cisatracurium that both provides adequate muscle relaxation during intubation and allows for reliable timely neuromonitoring interpretation has not been investigated.”

Comment 2: Page 5, line 70: I would not say that recurrent laryngeal nerve injury is a most common complication of thyroid surgery. I may hope it is not; better would be “RLN injury is a complication of great concern...”.

Reply 2: Thank you for your helpful suggestion. Actually, recurrent laryngeal nerve injury is the most severe complication of thyroid surgery, leading to transient or permanent voice changes, which among the most common causes of medical litigation (Sci Rep. 2018;8:7761). Laryngeal nerve injury is one of the most common complications of thyroid and parathyroid surgery (Ann Otol Rhinol Laryngol 2017 Jan;126(1):67-72). Insult to the RLN occurs in 0.3% to 13.2% of cases, whereas superior laryngeal nerve injury occurs in a relatively smaller proportion of patients (less than 5%) (Ann Otol Rhinol Laryngol 2017 Jan;126(1):67-72). Nevertheless, it may be more appropriate to describe RLN injury as a complication of great concern, as the reviewer suggests. We have revised this sentence to read, “Recurrent laryngeal nerve (RLN) injury is a complication of great concern during thyroid surgery.” (Please see page 5, line 72).

Changes in the text: “Recurrent laryngeal nerve (RLN) injury is a complication of great concern during thyroid surgery.”

Comment 3: Page 6, line 92: I once again refer to the authors’ statement about their own work. In this context they refer to –what the authors call- ‘recent’ studies with rocuronium. The authors are invited to look at their own references (15,16) that are from 2011 and 2016! Could be hardly called recent, I think!

Reply 3: Thank you for your helpful advice. We agree that this description was improper. We have replaced the word “recent” with “previous”. (Please see page 6, line 99).

Changes in the text: “Previous studies have investigated the dosage effect of rocuronium

on IONM (15,16).”

Comment 4: Page 8, line 143 (‘If unexpected difficult airway occurred because of poor muscle relaxation, patients were excluded from the study’) and Page 9, line 171 (‘If difficult intubation occurred because of insufficient muscle relaxation, an additional dose of cisatracurium was allowed, and the patients were excluded from the study’): I have a concern about this methodological statement by the authors. It would be of great importance if such an issue would have occurred (although it did not as far as I have read the results of this paper): it would have shown that, using a too low dose of an NMBA for intubation, may bring the patient in trouble. Exclusion out of the findings of an alike study would have been unfortunate.

Reply 4: We appreciate the reviewer’s concern. If unexpected difficult intubation occurs because of poor muscle relaxation, it is a critically important finding. The possibility of facing unexpected difficult airway was considered during our study design. In this situation, treatment with additional NMBA was required to improve intubation conditions, and intubation was carried out in accordance with the practice guidelines for difficult airway to ensure maximum patient safety. Therefore, these patients must be excluded from this study design and analysis. Nevertheless, this event should be documented in the Results. We have addressed this point in the revised manuscript. (Please see page 8, line 155 and page 10, line 187).

Changes in the text: “If unexpected difficult airway occurred because of poor muscle relaxation, an additional dose of cisatracurium was allowed to improve intubation conditions, patients were excluded from the study after documentation, and intubation was completed according to the guidelines of the American Society of Anesthesiologists (17).” “If difficult intubation occurred because of insufficient muscle relaxation, an additional dose of cisatracurium was allowed, and intubation was completed according to the practice guidelines for the management of the difficult airway by the American Society of Anesthesiologists (17). These patients were documented and then excluded from the study.”

Comment 5: Page 9, line 161: did your patients receive neuromuscular transmission monitoring before extubation of their tracheas? It is not because neuromonitoring was used intraoperatively, that the train-of-four ratio was higher than 0.90, before extubation.

Reply 5: Thank you very much for your question. Patients in our study received neuromuscular transmission monitoring in the postoperative anesthetic care unit before extubation. They were extubated after fulfilling extubation criteria (responding to verbal commands, achieving adequate spontaneous ventilation, and full recovery from muscle relaxation with a TOF ratio higher than 0.9). These are the standardized extubation

criteria for all patients in our institution. We have added the extubation criteria to the Methods section. (Please see page 9, line 175).

Changes in the text: “Patients were extubated after fulfilling extubation criteria (responding to verbal commands, achieving adequate spontaneous ventilation, and full recovery from muscle relaxation with a train-of-four ratio greater than 0.9 on neuromuscular transmission monitoring).”

Comment 6: Page 13-14: the discussion of the relaxing properties of inhaled anesthetics is futile here and should be deleted: it was no part of this study.

Reply 6: Thank you for your helpful suggestion. We have deleted this information from the Discussion. Please see the revised manuscript.

Comment 7: References: the authors are invited to check the Journal’s Guidelines for reference styling: look at the authors’ names in e.g. refs 3 and 4: the forenames have each time a different style (in full versus abbreviated).

Reply 7: Thank you for your helpful advice. We have checked the references and made the recommended changes in accordance with editorial requirements. (Please see the Reference section).

Comment 8: I would like to end up with drawing the attention of the authors to the fact that modern anesthesia tackles the problem of neuromonitoring during thyroid surgery by using rocuronium to facilitate tracheal intubation and, if necessary, followed by sugammadex, as a selective relaxant binding agent, to undo the interference of residual blocking effects when neuromonitoring is a necessity for intraoperative patient safety. The cost of sugammadex is in that case not only relative but unimportant, as patient safety has no price.

Reply 8: Thank you for your outstanding review. We have benefited greatly from the reviewer’s comments. We believe the reviewer makes a very good point that modern anesthetics are of great value in facilitating perioperative management of patients undergoing thyroid surgery with IONM. Intubation with rocuronium to achieve adequate muscle relaxation, followed by sugammadex to antagonize neuromuscular blockade to allow for early detection of IONM is of great help in this clinical situation. Guidelines recommend IONM in thyroid surgeries, especially those for thyroid cancer, in which the incidence of RLN injury is higher. However, sugammadex has not yet been introduced in our institution and hospital. Its relatively expensive cost has limited its clinical use in many institutions in China and in many other countries. At present, we are investigating appropriate alternatives for this specific clinical setting. We look forward to the day when

sugammadex is introduced in our institution and covered by health insurance. We believe patients will benefit enormously from this novel muscle relaxant antagonist.

### **Reviewer E**

Comment 1: Timing and dosage are both important to neuromuscular blockade (NMB) induced by cisatracurium. In a relative low dose of a NMBA, it may take up to 5 min to achieve maximal NMB. How did you decide the time point of tracheal intubation? by NMT monitor or by personal experience? This time point is crucial to intubation quality.

Reply 1: Thank you very much for your question, which makes a very good point. In our study, the time of tracheal intubation was decided according to the personal experience of the anesthesiologist in charge. We did not use NMT monitoring to guide the time of intubation because use of an NMT monitor could have provided hints to grouping information, which could have influenced the primary results of evaluation of intubation conditions and ease of intubation. Although we used objective scoring systems for these assessments, the evaluation was essentially subjective. In the current study, all tracheal intubations were performed by attending anesthesiologists with more than 10 years of clinical experience. Therefore, the assessment of primary results and tracheal intubation were reliable and effective. We have described this process in the Methods section. (Please see page 8, line 145).

Changes in the text: “Modified Cormack–Lehane classification was determined, and tracheal intubation was performed in the sniffing position with a Macintosh laryngoscope by an attending anesthesiologist with more than 10 years of clinical experience who was not involved in the detailed preoperative evaluation and who was blinded to group assignment. An endotracheal tube (Nerve Integrity Monitor, NIM; Medtronic, Jacksonville, Florida) was placed (size 6.0 for women and size 7.0 for men) after adequate muscle relaxation, which was evaluated on the basis of the clinician’s experience.”

Comment 2: One patient was excluded from the study because of the EMG signals loss. Did this event caused by malposition of EMG tube, RLN injury or improper NMB? It needs further discussion.

Reply 2: Thank you for your question and advice. One patient was excluded from the study because the EMG signals were lost during surgery. During surgery, this patient was found to have recurrent laryngeal nerve invasion requiring unilateral recurrent laryngeal nerve resection to achieve complete tumor resection. We have described the details of this patient in the Results section. (Please see page 12, line 240).

Changes in the text: “During surgery, this patient was found to have RLN invasion that required unilateral RLN resection to achieve complete tumor resection.”

Comment 3: In C2 group, the lowest and median EMG is 181 and 448  $\mu$ V respectively. In many IONM literatures (i.e. Laryngoscope. 2020 Apr;130(4):E280-E283, J Invest Surg. 2020 Aug 14:1-8, Kaohsiung J Med Sci. 2020 Apr;36(4):230-235), NMBA regimen with initial high EMG amplitude is important and helpful to surgeons to identify intraoperative signal reduction. It is welcome to describe this drawback of cisatracurim in the limitations.

Reply 3: Thank you for your advice. We agree that high initial EMG amplitude is important and helps surgeons to identify intraoperative signal reduction (Kaohsiung J Med Sci. 2020 Apr;36(4):230-235). In our study, all patients in both groups had a positive EMG signal of  $> 100 \mu$ V at initial monitoring; the amplitude of V1 was not significantly different between the two groups. However, the lowest and median EMG signals in group C2 were 181 and 448  $\mu$ V, respectively, which are lower than the recommended high initial EMG amplitude of  $> 500 \mu$ V. In groups C1 and C2, the initial monitoring started at  $39.7 \pm 7.8$  min and  $38.2 \pm 7.5$  min, respectively, after administration of cisatracurium. These time intervals were shorter than some of those reported in previous studies. Several factors besides neuromuscular blockade may also alter the amplitude of EMG signals, which may partly explain why the amplitude has varied greatly among previous studies. Recent studies have also demonstrated that the EMG signals obtained from needle electrodes on the thyroid cartilage were significantly higher than those from the EMG tube (Laryngoscope. 2020 Apr;130(4):E280-E283). Still, we agree with the reviewer that the lower V1 amplitudes were most likely caused by the use of cisatracurium in our study. Cisatracurium is a double-edged sword in this specific clinical setting because better EMG signals are achieved with a smaller dosage of NMBA at the expense of less favorable intubation conditions. The opposite is also true. This drawback is clinically inevitable to achieve better intubation conditions. Therefore, various factors need to be weighed individually during clinical management. We have addressed these issues in the Discussion. (Please see page 15, line 309 and page 17, line 336).

Changes in the text: "In previous studies of rocuronium,  $1 \times$  the ED<sub>95</sub> of rocuronium was recommended to guarantee sufficient recovery of neuromuscular transmission for IONM (15,16, Laryngoscope 2020;130(4):E280-E283, Kaohsiung J Med Sci 2020;36(4):230-235). However, a lower degree of neuromuscular block resulted in less favorable intubation conditions (20)." "Finally, a high initial EMG amplitude (V1) is recommended for correct interpretation and verification of intact RLN function (3, Laryngoscope 2020;130(4):E280-E283). Although all patients in the present study had a positive signal of  $> 100 \mu$ V at initial monitoring and the amplitude of V1 was comparable between the two groups, the median EMG of V1 in group C2 was slightly lower than the recommended high initial EMG amplitude of  $> 500 \mu$ V. This is a drawback that must be evaluated individually in this specific clinical setting. Better EMG signals are achieved with a smaller dosage of NMBA at the expense of less favorable intubation conditions;

the opposite is also true.”

Comment 4: Related to tracheal intubation, the definition of intubation time and first-attempt success rate required clear description.

Reply 4: Thank you for your suggestion. The intubation time was recorded as the time from insertion of the laryngoscope to the appearance of an end-tidal carbon dioxide trace on capnography. One patient in each group had two intubation attempts and both were finally intubated with a Shikani optical stylet because of difficult laryngoscopy despite the assistance of external laryngeal pressure. The first-attempt success rate was 96.2% in both groups. We have included this information in the revised manuscript. (Please see page 10, line 193 and page 13, line 261).

Changes in the text: “Intubation time was recorded as time from insertion of the laryngoscope to the appearance of an end-tidal carbon dioxide trace on capnography.”  
“The first-attempt success rate was 96.2% in both groups.”