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ORIGINAL ARTICLE

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Investigation of potential neuropharmacological activity of neostigmine-glycopyrrolate for intraoperative neural monitoring in thyroid surgery

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Abstract

Intraoperative neuromonitoring (IONM) is frequently used in thyroid surgery to reduce recurrent laryngeal nerve injury. The use of neuromuscular blockade agent to facilitate tracheal intubation, is a common cause of IONM failure. We performed a retrospective analysis to assess the efficacy of neostigmine-glycopyrrolate as a neuromuscular blockade reversal agent for IONM during thyroid surgery. Rocuronium (0.6 mg/kg) was administered for muscle relaxation. Neostigmine (2 mg) and glycopyrrolate (0.4 mg) were administered immediately after intubation. Cricothyroid muscle-twitch response upon external branch of superior laryngeal nerve stimulation and electromyography amplitudes of vagal and recurrent laryngeal nerves before (V1, R1) and after thyroid resection (V2, R2) were recorded. Fifty patients (23 males, 27 females) were included in the analysis. The diagnoses comprised 43 papillary thyroid carcinomas and seven benign diseases. The mean time between rocuronium injection and neostigmine-glycopyrrolate injection was 5.1 ± 1.2 min, and the mean time from neostigmine-glycopyrrolate injection to successful cricothyroid muscle twitching upon external branch of superior laryngeal nerve stimulation was 21.0

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± 4.5 min. All patients had V1 and R1 amplitudes of more than 500 μV each, with mean V1 and R1 amplitudes of 985.3 ± 471.6 μV and 1177.2 ± 572.7 μV, respectively. Neostigmine-glycopyrrolate was effectively used as a neuromuscular blockade reversal agent for IONM in thyroid surgeries without a significant increase in bucking events. Administration of neostigmine-glycopyrrolate immediately after intubation can be recommended for successful NMB reversal to facilitate IONM during thyroid surgery.

KEYWORDS
glycopyrrolate, neostigmine, neuromuscular blockade, neuromuscular monitoring, thyroidectomy

1 | INTRODUCTION

In recent years, the use of intraoperative neuromonitoring (IONM) has increased in thyroid surgery and become standard practice in high-risk cases because it facilitates direct visualization and rapid identification of the RLN, allows detection of anatomic variations, and reduces the risk of RLN injury.[1–3]

Correct management and titration of the neuromuscular blockade (NMB) are important in successful neural monitoring.[4] Adequate NMB is necessary for tracheal intubation and muscle relaxation. Timely restoration of neuromuscular function is required for neuromonitoring signals.[5] Various strategies for NMB management include relaxant-free anesthesia, lower doses of NMB agents, and regular doses of NMB agents with sugammadex.[6–8] Sugammadex has been reported to be the most effective drug for IONM because of its rapid and predictable reversal of NMB.[9] However, the high cost of sugammadex limits its adoption as a standard NMB reversal agent in most countries' healthcare systems.[10,11]

Co-administered neostigmine and glycopyrrolate is a popular and widely used alternative NMB reversal method.[12] Neostigmine is an acetylcholinesterase inhibitor that interferes with the breakdown of acetylcholine to promote the impulse transmission between neuromuscular junctions and antagonize the residual effect of muscle relaxants. Glycopyrrolate is an anticholinergic drug to counteract the muscarinic actions of neostigmine.[13] Although neostigmine-glycopyrrolate is a safe, effective, and inexpensive drug combination for NMB reversal, a standardized approach for its application for IONM during thyroid surgery has not been established.[14] In this study, we report our experience using neostigmine-glycopyrrolate as a NMB reversal agent for IONM during thyroid surgery.

2 | METHODS

2.1 | Patients

A retrospective analysis of prospectively collected data was done of patients who underwent thyroidectomy using IONM after neostigmine-glycopyrrolate administration at OOO between December 2020 and March 2021. Patients who underwent endoscopic or robotic thyroid surgeries were excluded. This study was approved by the Institutional Review Board of the OOO (IRB number: 20-2021-13).

2.2 | Induction and maintenance of anesthesia

Anesthesia was induced with injections of lidocaine (30 mg) followed by propofol (1.5 mg/kg) and maintained with a target-controlled infusions of propofol and remifentanil using infusion pumps. After loss of consciousness, rocuronium (0.6 mg/kg) was administered for muscle relaxation. A surgical pillow was placed beneath the neck for positioning prior to intubation to prevent inadvertent tube displacement during positioning.[15] Endotracheal intubation was performed using electromyographic (EMG) endotracheal tubes (Medtronic, Jacksonville, Florida) with the surface electrodes on the tube placed at the level of the vocal cords. Immediately after tube fixation, a combination of neostigmine (2 mg) and glycopyrrolate (0.4 mg) was administered. The times of rocuronium injection, intubation, and neostigmine-glycopyrrolate injection were recorded. All anesthetic procedures were performed or supervised by a single anesthesiologist (J.L).

2.3 | Intraoperative neuromonitoring

Nerve monitoring was performed in accordance with the International Neural Monitoring Study Group (INMSG) guidelines.[16] Nerve integrity monitoring (NIM) was performed using the NIM-response 3.0 system (Medtronic, Jacksonville, Florida). The stimulation duration was set to 100 ms, the event threshold was set to 100 mV, and the stimulus current was set to 1 mA with a frequency of 4 Hz. The cutoff value for the vagus nerve (VN) response and recurrent laryngeal nerve (RLN) response was set at 100 μV. To assess recovery from NMB, a train-of-four (TOF) peripheral nerve stimulator monitoring device (IDMED, Marseille, France) was placed between the patient's index finger and thumb (adductor pollicis muscle).[17] The TOF count refers to the number of detected muscle contraction responses when four sequential supramaximal stimuli are generated at 0.5 s intervals. The results were recorded as the number of responses per four stimuli given (0/4, 1/4, 2/4, 3/4, 4/4) with a lower TOF count indicating a higher level of neuromuscular block. TOFr ratio (TOFr) refers to the ratio of the fourth muscle response to the first one and indicates fade in nondepolarizing block. Because all four responses to each of the stimuli are needed to measure TOFr, the TOFr was calculated for a TOF count of 4/4.[18]

2.4 | Operative procedures and outcome measurement

Surgery was performed by a single surgeon (Y.J.C). A low-collar neck incision was made along the skin crease, and the incision time was recorded. After flap dissection, the strap muscles were separated from the thyroid gland, and the upper pole of the thyroid gland was exposed. Electrical stimulation of the external branch of super laryngeal nerve (EBSLN) was made with a monopolar nerve stimulator probe (Prass Standard Monopolar Stimulator Probe, Medtronic, Jacksonville, Florida) at 1 mA to evoke cricothyroid muscle contraction. Muscular response to stimulation was evaluated and recorded as "absent" or "present" depending on the cricothyroid muscle-twitch response. If no twitch-response was observed, the electrical stimulation was increased to 2 mA and reapplied. If there was still no twitch-response at 2 mA, stimulation was applied in 2-min intervals until muscular response was observed. The time and TOF ratio (TOFr) for each stimulation were recorded.

Nerve stimulation of the VN and RLN were routinely carried out before and after resection. The V1 and R1 signals were defined as the initial EMG signal from the VN and RLN, respectively, before initiating thyroid resection. The R2 and V2 signals were defined as the EMG signals of the RLN and VN, respectively, after thyroid resection. Upper pole dissection was completed under EBSLN monitoring. The carotid sheath was dissected to expose the VN which was stimulated at 1 mA to obtain the V1 signal. The RLN was identified and stimulated at 1 mA to obtain the R1 signal. The amplitude, time at stimulation, and TOFr were recorded for both V1 and R1. After thyroid resection, V2 and R2 signal amplitudes, time at stimulation, and TOFr were similarly recorded. In patients who underwent total thyroidectomy, only the results of the lobe that was approached first were recorded. The surgeon suspended the operation and resumed after 1 min if there was significant patient movement or bucking during surgery. The time of each bucking event was recorded.

2.5 | Statistical analysis

The data are presented as mean ± SD or as the median for continuous variables depending on the normality of data distribution. Categorical variables were analyzed by the chi-square test or Fisher's exact test. Two tailed values of $p < 0.05$ were deemed statistically significant. All statistical analyses were performed using SPSS 26.0 software for Windows (IBM, Armonk, New York).

3 | RESULTS

Fifty patients (23 males and 27 females) were included in the study. The mean age was 53.7 ± 12.9 years, and the mean body mass index was 25.6 ± 4.0. The mean tumor size was 1.1 ± 0.8 cm. Of the 50 patients, 42 (84.0%) underwent lobectomy and eight (16.0%) underwent total thyroidectomy. The final pathological diagnoses comprised 43 papillary thyroid carcinomas, and seven benign diseases (three Hurthle cell adenomas, two Graves' diseases, one follicular adenoma, and one Hashimoto's thyroiditis). The mean operative time was 53.4 ± 10.2 min (Table 1).

Table 2 shows the timeline of the anesthetic and operative procedures. The mean time from rocuronium injection to neostigmine-glycopyrrolate injection was 5.1 ± 1.2 min, and the mean time from neostigmine-glycopyrrolate injection to EBSLN stimulation was 21.0 ± 4.5 min. There were three bucking events in two patients (one bucking event in one patient and two bucking events in the other). The mean time from neostigmine-glycopyrrolate injection to the first bucking event was 13.8 ± 12.4 min (Table 2).

The IONM outcomes are presented in Table 3. At EBSLN stimulation, TOF count was 0/4 in 10 (20%) patients, 1/4 in 10 (20%) patients, 2/4 in six (12%) patients, and 3/4 in two (4%) patients. The remaining 22 (44%) patients reached a TOF of 4/4 with a mean TOFr of 48.0 ± 24.9%. Cricothyroid muscle twitch-response upon first EBSLN stimulation was absent in three (6%) patients. An increased stimulation of 2 mA was applied two times additionally at 2-min intervals before a "present" response was evoked. At V1, the TOF count was 0/4 in eight (16%) patients, 1/4 in eight (16%) patients, 2/4 in

TABLE 1 Patient characteristics

Patient characteristics	Total patients ($N = 50$)
Gender (male: female)	23:27
Age (years)	53.7 ± 12.9
Body mass index (kg/m^2)	25.6 ± 4.0
Tumor size in longest diameter (cm)	1.1 ± 0.8
Extent of operation	
Lobectomy	42 (84.0%)
Total thyroidectomy	8 (16.0%)
Diagnosis	
Papillary thyroid carcinoma	43 (86.0%)
Hurthle cell adenoma	3 (6.0%)
Graves' disease	2 (4.0%)
Follicular adenoma	1 (2.0%)
Hasimoto's thyroiditis	1 (2.0%)
Operative time (min)	53.4 ± 10.2

Note: All data are presented as mean ± SD or as n (%), unless stated otherwise.

TABLE 2 Timeline of anesthetic and operative procedures

Description	Time interval in minutes
Rocuronium to neostigmine-glycopyrrolate	5.1 ± 1.2
Neostigmine-glycopyrrolate to skin incision	7.7 ± 3.2
Neostigmine-glycopyrrolate to EBSLN stimulation	21.0 ± 4.5
Neostigmine-glycopyrrolate to V1	26.1 ± 5.5
Neostigmine-glycopyrrolate to R1	28.6 ± 6.0
Neostigmine-glycopyrrolate to R2 and V2	41.8 ± 10.0
Neostigmine-glycopyrrolate to first bucking event (if any)	13.8 ± 12.4

Note: All data are presented as mean ± SD.
Abbreviations: EBSLN, external branch of the superior laryngeal nerve; R1, initial electromyography signal of the recurrent laryngeal nerve upon its initial identification; R2, electromyography signal of the recurrent laryngeal nerve after thyroidectomy; V1, initial electromyography signal of the vagus nerve before surgical dissection; V2, electromyography signal of the vagus nerve after thyroidectomy.

TABLE 3 Outcomes of intraoperative neuromonitoring

Description	Total patients (*N* = 50)
EBSLN stimulation	
TOFr (0/4, 1/4, 2/4, 3/4, 4/4)	10/10/6/2/22
TOFr, % for 4/4 (*n* = 22)	48.0 ± 24.9
Cricothyroid muscle response on first stimulation	
Present	47 (94.0%)
Absent	3 (6.0%)
V1	
TOFr (0/4, 1/4, 2/4, 3/4, 4/4)	8 / 8 / 2 / 1 / 31
TOFr, % for 4/4 (*n* = 31)	53.2 ± 24.2
Amplitude of, μV (range)	985.3 ± 471.6 (504–2944)
R1	
TOFr (0/4, 1/4, 2/4, 3/4, 4/4)	8 / 9 / 3 / 1 / 29
TOFr, % for 4/4 (n = 29)	62.8 ± 20.9
Amplitude, μV (range)	1177.2 ± 572.7 (537–2889)
R2 and V2	
TOFr (0/4, 1/4, 2/4, 3/4, 4/4)	2 / 2 / 3 / 2 / 41
TOFr, % for 4/4 (n = 41)	75.1 ± 18.9
Amplitude of R2, μV (range)	1195.5 ± 618.2 (508–2952)
Amplitude of V2, μV (range)	898.1 ± 437.1 (516–2597)
Bucking events	2 (4.0%)

Note: All data are presented as mean ± SD or as n (%), unless stated otherwise.
Abbreviations: EBSLN, external branch of the superior laryngeal nerve; R1, initial electromyography signal of the recurrent laryngeal nerve at its initial identification; R2, electromyography signal of the recurrent laryngeal nerve after thyroidectomy; RLN, recurrent laryngeal nerve; TOFr, Train-of-Four ratio; V1, initial electromyography signal of the vagus nerve before surgical dissection; V2, electromyography signal of the vagus nerve after thryoidectomy.

two (4%) patients, and 3/4 in one (2%) patient. Of the 31 (62%) patients who reached a TOF of 4/4, the mean TOFr was 53.2 ± 24.2%. All patients had V1 amplitudes of more than 500 μV, with a mean V1 amplitude of 985.3 ± 471.6 μV (504–2944 μV). At R1 stimulation, the TOF count was 0/4 in eight (16%) patients, 1/4 in nine (18%) patients, 2/4 in three (6%) patients, and 3/4 in one (2%) patient. There were 29 (58%) patients who had a TOF count of 4/4, and in this group, the mean TOFr was 62.8 ± 20.9%. All patients had R1 amplitudes of more than 500 μV, with a mean R1 amplitude of 1177.2 ± 572.7 (537–2889 μV). At the R2 and V2 time points, the TOF count was 0/4 in two (4%) patients, 1/4 in two (4%) patients, 2/4 in three (6%) patients, and 3/4 in two (4%) patients. There were 41 patients with a TOF count of 4/4, and in this group the mean TOFr was 75.1 ± 18.9%. All patients had R2 amplitudes of more than 500 μV, with a mean R2 amplitude of 1195.5 ± 618.2 μV (508–2952 μV). All patients had V2 amplitudes of more than 500 μV, and the mean V2 amplitude was 898.1 ± 437.1 μV (516–2597 μV; Table 3). There was no case of recurrent laryngeal nerve injury. There were no side effects related to neostigmine.

4 | DISCUSSION

This study explored the use of neostigmine-glycopyrrolate as a NMB reversal agent to assess its effect on the quality of IONM for thyroid surgery. In patients who received neostigmine-glycopyrrolate co-administration immediately following intubation, the average time to cricothyroid muscle twitch-response upon EBSLN stimulation was 21.0 ± 4.5 min from neostigmine-glycopyrrolate injection. Two studies have demonstrated the adequacy of IONM when no reversal agents were used: Marshall et al.[19] reported that an average of 44.6 min from NMB agent injection to R1, and Gunes et al.[20] reported an average of 50 min from NMB agent injection to V1. In a study comparing different doses of sugammadex as a reversal agent for IONM in thyroid surgeries, the reported average time from sugammadex injection to EBSLN stimulation was 25.0–25.5 min.[21] The current study suggests that neostigmine-glycopyrrolate may induce faster NMB reversal compared to no reversal agents and may have comparable effects to that of sugammadex.

Sugammadex, a selective relaxant-binding agent, was specifically developed for rapid reversal of rocuronium-induced NMB.[22] By selectively binding to NMB agents, sugammadex inactivates free NMB agents in the plasma, resulting in a large concentration gradient of NMB agent molecules between the neuromuscular junction and the plasma, leading to decreased NMB agents at the neuromuscular junction end plate.[23] This mechanism allows neuromuscular transmission to resume in a short period of time, making it a more popular drug for IONM compared with other reversal agents.[24] Unfortunately, the high cost of sugammadex have precluded its use as the standard NMB reversal agent in most healthcare systems.[10] The prices of sugammadex and neostigmine-glycopyrrolate were US$ 95 and US$ 0.8, respectively. Alternative available cost-effective options, such as neostigmine-glycopyrrolate, need to be explored.

Arousal during surgery is potentially dangerous because sudden unexpected patient movements can result in injury to important structures, lead to bleeding, and interrupt or delay surgical procedures. While NMB reversal is crucial for IONM, maintaining adequate muscle relaxation during surgery is even more important. Because sugammadex allows faster return of muscle activity, bucking and movement during surgery are the most frequently reported adverse effects associated its use.[23] In fact, studies have reported that 20–35% of patients administered sugammadex (2 mg/kg) as a reversal agent for IONM had bucking events during surgery.[7,21] Even when the dose of sugammadex was reduced to 1 mg/kg, bucking events were noted in 14% of the patients.[21] In this study, bucking events were observed in only two (4%) patients. Although slower to act than sugammadex, neostigmine seems to reverse the NMB quickly enough for IONM with less unwanted movement and bucking events during surgery. However, further comparative studies on the two reversal agents are needed to prove that neostigmine minimizes unexpected intraoperative patient movements.

Neostigmine can cause some adverse effects, most of which are due to the drug's cholinergic effects, including bradyarrythmias, bronchospasm, increased secretions, nausea, and vomiting. However, many of the adverse effects can be reduced with a concurrent administration of glycopyrrolate, an anticholinergic drug.[13] None of the patients in our study experienced any side effects related to neostigmine. Some studies showed that there is no significant difference in the critical respiratory events and postoperative nausea and vomiting between sugammadex and neogstigmine-glycopyrrolate.[12,25]

TOF monitoring with a peripheral nerve stimulator is used to assess the recovery of neuromuscular transmission at the adductor pollicis muscle. The adductor pollicis muscle has the slowest recovery among all the muscles, thus recovery of neuromuscular transmission in this muscle indicates recovery of respiration and airway protective reflexes.[26] While TOF monitoring may have advantages in evaluating the adequacy of neuromuscular recovery for determining when to extubate after surgery, the appropriateness of its use for IONM during thyroid surgery is debatable. In this study, the cricothyroid muscle twitch-response and V1, and R1 signals were present even when TOFr was <4/4. Furthermore, the mean amplitudes of V1 and R1 were 985.3 ± 471.6 μV and 1177.2 ± 572.7 μV, respectively, while eight (16.0%) of the 50 patients still had a TOFr of 0%. This was expected as the reversal of NMB varies depending on the muscle type.[26,27] Therefore, TOF monitoring may be of little value in IONM, and results should be carefully interpreted when NMB reversal is evaluated during thyroid surgery.

In this study, we measured the time from neostigmine-glycopyrrolate injection to the first positive cricothyroid muscle twitch-response upon EBSLN stimulation. The EBSLN innervates the cricothyroid muscle which adjusts the tension and length of the vocal cords.[26] Injury to the structure causes difficulties in producing high-pitched sounds, change in the voice frequency, and voice fatigue.[28] The risk of EBSLN injury is high during thyroidectomy due to its close anatomical relationship with the superior thyroid vessels. The use of IONM significantly improves the EBSLN identification rate, and reduces the risk of phonation changes after surgery.[29] While IONM for EBSLN is becoming more common, unlike the routine dissection of the RLN, many surgeons tend not to routinely use IONM for EBSLN.[30] Although V1 and R1 signals are commonly used in IONM studies for thyroid surgery, EBSLN stimulation is quite uncommon. We included these results in our study because in most cases, the EBSLN is approached before the VN and RLN, and we believe that IONM to protect the EBSLN is just as important as the RLN. Because IONM helps the visual and functional identification of the EBSLN and decreases the rate of EBSLN injury, the routine use of IONM for EBSLN is encouraged.[31,32]

There are limitations in this study. First, this is a retrospective observational study, and as an uncontrolled study, there may have been variables that the patients may have been exposed to that may have affected the results. Second, this study has a small sample size. A larger sample size is needed to reduce the potential for variation in drug responses to rocuronium and neostigmine-glycopyrrolate. Despite the small sample size, this study showed only 21.0 ± 4.5 min from neostigmine-glycopyrrolate injection until response to EBSLN stimulation, indicating that neostigmine-glycopyrrolate can reverse NMB rapidly enough for IONM to be effective during thyroid surgery. Last, this study is not a comparison study without a control "no reversal agent" group. This study does not show how much faster neostigmine-glycopyrrolate reverses NMB compared to when no reversal agents are given, and how it affects the surgical procedure in terms of unwanted movement or bucking during surgery due to faster reversal of NMB compared to a control group. Nevertheless, considering that only two (4%) patients experienced bucking events when neostigmine-glycopyrrolate was administered immediately after intubation, it seems that administering neostigmine-glycopyrrolate directly after intubation makes IONM possible without many complications. Comparative studies are needed in the future.

When neostigmine-glycopyrrolate was used as a reversal agent, cricothyroid muscle twitch-response upon EBSLN simulation was detected on first evaluation for all but two patients and took a mean time of 21.0 ± 4.5 min from rocuronium to detection of EBSLN response. The V1 and R1 signal amplitudes of all patients were over 500 μV, and bucking events occurred in only two patients. These results suggest that neostigmine-glycopyrrolate immediately after intubation can be effectively used as a reversal agent for successful IONM in thyroid surgery.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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