The Laryngoscope

Optimal Anesthetic Regimen for Ambulatory Laser Microlaryngeal Surgery

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Objectives/Hypothesis: Laser microlaryngeal surgery (LMS) is a short operation requiring brief and intense paralysis. Adequate muscle relaxation and rapid recovery of neuromuscular function are essential for improving surgical conditions and reducing the incidence of complications during LMS. However, the ideal muscle relaxant with a rapid onset and short duration of action is not yet available. Rocuronium has rapid onset at higher doses, but with a prolonged duration of action. Sugammadex is a selective relaxant-binding agent that allows for rapid reversal of rocuronium-induced neuromuscular blockade. This study aimed to compare the surgical conditions and anesthesia time between two combinations of neuromuscular blocker and reversal agent, rocuronium-sugammadex (R-S) and succinylcholine-cisatracurium-pyridostigmine (S-C-P), and propose an optimal anesthetic regimen for improving the surgical conditions in LMS patients.

Study Design: Prospective, randomized, double-blinded clinical study.

Methods: Patients in the R-S group received 1 mg/kg rocuronium bromide, whereas those in the S-C-P group received 1 mg/kg succinylcholine. After endotracheal intubation, 0.08 mg/kg cisatracurium was injected in S-C-P patients. After the procedure, R-S patients received 2 mg/kg sugammedex, whereas S-C-P patients received 0.2 mg/kg pyridostigmine plus 10 μg/kg atropine.

Results: In the R-S group, surgical condition scores were significantly higher and anesthesia time was significantly shorter. The use of additive neuromuscular blocking agents was significantly higher in the S-C-P group.

Conclusions: Muscle relaxation with rocuronium and reversal with sugammadex resulted in better surgical conditions and a shorter anesthesia time in patients undergoing LMS when compared to the S-C-P regimen.

Key Words: Laser microlaryngeal surgery, rocuronium, succinylcholine, sugammadex, surgical condition.

Level of Evidence: 1b

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INTRODUCTION

Laser microlaryngeal surgery (LMS) is a commonly performed, minimally invasive procedure used in otolaryngology and head and neck surgery for the diagnosis and treatment of laryngeal pathologies.[1] LMS is a short operation that requires a brief and deep neuromuscular blockade. If the patient is moving or the vocal cords are not fully paralyzed, scarring of the laryngeal mucosa or vocal cord trauma may result.[2] Any minor trauma during the operation can be extremely harmful and may result in a catastrophic outcome. Therefore, adequate muscle relaxation is essential during LMS. Furthermore, deep neuromuscular blockade offers the surgeon an ideal view and leads to a lower incidence of complications. Because LMS is a highly sophisticated operation, deep neuromuscular blockade is required for full visualization of the larynx and vocal cords. In addition, the diaphragm and laryngeal adductor muscles are more resistant to nondepolarizing neuromuscular blocking agents (NMBAs) than the adductor pollicis, and complete paralysis of these muscles is not expected with a dose that barely blocks the adductor pollicis.[3] For this reason, disappearance of the train-of-four (TOF) at the adductor pollicis does not completely eliminate the possibility of hiccups, cough, or vocal cord movement, and the surgical conditions might be different from those expected by anesthesiologists. Therefore, more intense neuromuscular blockade is required for improving the surgical conditions and reducing the complication. However, the ideal muscle relaxant, with rapid onset time, short duration of action, and minimal side effects, is not yet available.[4]

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TABLE I.
Laser Microlaryngeal Surgery Surgical Rating Scale.

Score	Definition
1. Extremely poor conditions	Inability to obtain a visible laryngeal field with coughing or movement
2. Poor conditions	Visible laryngeal field with continuous movements
3. Acceptable conditions	Visible laryngeal field with sporadic movements
4. Good conditions	Visible laryngeal field without any coughing or movement
5. Optimal conditions	Wide visible laryngeal field without any coughing or movement

Succinylcholine is a muscle relaxant commonly used during LMS because of its rapid onset time and short duration of action.[5] In short surgical procedures like LMS, the use of succinylcholine for tracheal intubation is usually followed by a succinylcholine drip[6] or small boluses of an intermediate-duration nondepolarizing NMBA. However, succinylcholine has many adverse side effects, such as profound cardiovascular alteration, hyperkalemia, myoglobulinemia, and myalgia, as well as increased gastric, intracranial, and intraocular pressures.[4,5] Continuous succinylcholine infusion of 90 minutes or less has been reported to induce phase II neuromuscular block.[7,8] Even a single bolus of succinylcholine can cause complications.[9,10]

Rocuronium is used as an alternative to succinylcholine during LMS. The onset of 1 mg/kg rocuronium is ~60 seconds, which is similar to that of succinylcholine.[6] However, higher doses of rocuronium have a longer duration of action, which is inappropriate in ambulatory surgery, which requires rapid recovery of neuromuscular function and rapid turnover.[5] Sugammadex has recently been introduced as a selective relaxant-binding agent that allows for rapid reversal of rocuronium-induced neuromuscular blockade. Even deep or profound neuromuscular block with rocuronium can be quickly antagonized with sugammadex.[11] Several studies have reported successful use of rocuronium-sugammadex (R-S) as an alternative to succinylcholine during rapid sequence intubation[6,12] and electroconvulsive therapy.[5,7]

However, there has been no investigation of the use of a neuromuscular blocker and reversal agent regimen as an alternative to succinylcholine during LMS. We hypothesized that R-S may be an alternative to succinylcholine during LMS, and R-S may permit good surgical condition and not delay recovery time. Thus, the primary objective of the present study was to compare the surgical condition between the succinylcholine-cisatracurium-pyridostigmine (S-C-P) regimen and the R-S regimen. The secondary objective was to compare the recovery time between the two regimens.

MATERIALS AND METHODS

This study was approved by the institutional review board of Korea University Medical Center (ED14030) and is registered at ClinicalTrial.gov (NCT02329964). After obtaining written informed consent from each patient, 80 patients (American Society of Anesthesiologists physical status I or II, age >18 years) undergoing scheduled LMS under general anesthesia were included in this study. Exclusion criteria were suspected difficult tracheal intubation; any disorder affecting neuromuscular blockade; known or suspected severe hepatic dysfunction; a history of malignant hyperthermia; allergy to opioids, NMBAs, or other medications used during general anesthesia; contraindication to pyridostigmine and/or atropine; use of aminoglycoside antibiotics or oral contraceptives; pregnancy or breastfeeding; and body mass index >27 kg/m^2.

The patients were randomly assigned to either the S-C-P (n = 40) or R-S group (n = 40) using a computer-generated randomization method. Because this was a double-blind study, all patients, the anesthetic providers, and the investigators collecting the data were blinded to the study group assignments. An independent researcher prepared syringes containing the study drugs.

The patients were monitored using electrocardiography, noninvasive arterial pressure measurements, pulse oximetry, and capnography. Anesthesia was induced with intravenous propofol (1.5–2.5 mg/kg), together with 1.5 μg/kg fentanyl. After induction of anesthesia, continuous neuromuscular monitoring was performed at the adductor pollicis muscle using a TOF-Watch monitor (Organon, Roseland, NJ). Subsequently, patients in the S-C-P group received 1 mg/kg succinylcholine, whereas R-S patients received 1 mg/kg rocuronium bromide (Esmeron; Merck Sharp and Dohme, Oss, the Netherlands). Mask ventilation was initiated with 100% oxygen. After the first TOF twitch was assessed as 0 by the neuromuscular monitor, endotracheal intubation was performed. After endotracheal intubation, 0.08 mg/kg cisatracurium was injected in S-C-P patients, and the same volume of normal saline was injected in R-S patients. Anesthesia was maintained with desflurane, and hypnotic depth was kept in the range of 45 to 55 using BIS VISTA (Aspect Medical Systems, Inc., Norwood, MA). The lungs were ventilated with a tidal volume of 8 to 10 mL/kg at a respiratory rate of 8 to 12 breaths/min in 50% oxygen with air to maintain end-tidal CO_2 within the range of 30 to 35 mm Hg. An additive dose of 10 mg succinylcholine or 0.15 mg/kg rocuronium was administered as necessary to ensure that the neuromuscular blockade remained below the second TOF twitch during surgery or as required by the surgeon to improve the surgical conditions.

When the surgical procedure was finished, patients in the R-S group received 2 mg/kg sugammadex (Bridion; Merck Sharp and Dohme), and the same volume of normal saline was injected in the S-C-P group. When the second TOF twitch appeared, 0.2 mg/kg pyridostigmine plus 10 μg/kg atropine were administered as reversal agents in the S-C-P group, and patients in the R-S group were administered the same volume of normal saline. The time from the end of the operation to the administration of the reversal agent was recorded in the S-C-P group. The time from the administration of the reversal agent to the recovery of the TOF ratio to 0.1 and 0.9, the first spontaneous breath, opening of the eyes to verbal commands, and extubation was also recorded. A single surgeon scored the surgical conditions after the operation using a 5-point scale from 1 (extremely poor) to 5 (optimal) (Table I). The operation time, anesthesia time, and length of stay in the operating room were recorded. The end of the operation was defined as the time when the direct laryngoscope, aided by an operation microscope, was removed.

During the postoperative period, an investigator blinded to the study group assignment assessed each patient for clinical evidence of residual or recurrent neuromuscular blockade. A

TABLE II.
Demographic Data.

Characteristic	R-S group (n = 40)	S-C-P group (n = 40)	P
Gender, male/female, no.	22/18	24/16	.821
Age, yr	48 ± 12	52 ± 15	.175
Height, cm	164.7 ± 8.8	168.0 ± 7.6	.095
Weight, kg	66.4 ± 14.6	67.3 ± 8.0	.810
Operation time, min	12.2 ± 5.1	14.1 ± 7.5	.198

Values are reported as mean ± standard deviation unless indicated otherwise.
R-S = rocuronium-sugammadex; S-C-P = succinylcholine-cisatracurium-pyridostigmine.

surgeon (S.-K.B.) was informed of the hypothesis of the present study and understood the impact of the anesthetic technique on surgery. He was blinded to the study group assignment and scored the surgical conditions after the operation using a 5-point scale from 1 (extremely poor) to 5 (optimal) (Table I).

Neuromuscular Assessment

Neuromuscular monitoring was performed using a TOF-Watch monitor. The ulnar nerve was supramaximally stimulated near the wrist with square pulses of 0.2 ms duration, delivered as TOF pulses of 2 Hz at 15-second intervals. The resulting contractions of the adductor pollicis muscle were quantified using an acceleromyography monitor.

Statistical Analysis

Sample size. Based on a previous study showing that patients receiving sugammadex recovered 3.4 times faster than patients receiving pyridostigmine,[8] a sample size of 35 patients per group was calculated to detect with 90% power a 6-minute difference in recovery time of T1 to 90% between the groups at an α level of .05 using an independent t test. In this study, 40 patients in each group were recruited to allow for a possible 15% dropout rate during the study period.

Primary Hypothesis Testing

The normality of the data distribution was assessed using q-q plots and Shapiro-Wilk tests. Parametric data were analyzed using the independent t test. Nonparametric data were compared using the Mann-Whitney test. Statistical differences between the groups were evaluated by the χ^2 or Fisher exact tests as appropriate. All values are expressed as mean (± standard deviation), median (interquartile range), or number of patients. P values $<.05$ were considered statistically significant.

RESULTS

In total, 80 patients participated in this study (S-C-P group, n = 40; R-S group, n = 40). Demographic characteristics were similar between groups (Table II).

During anesthetic induction, the time from the administration of NMBAs to a T1 of 0 was similar between groups (89 ± 37 seconds vs. 108 ± 74 seconds; $P = .173$). Additive NMBAs were required significantly more often in the S-C-P group (20 of 40 patients) than in the R-S group ($P < .001$; Table III). There was no significant difference in the time from the start of reversal agent administration to recovery of the TOF ratio to 0.1 and 0.9 or time to the first spontaneous breath, eye opening, and extubation (all $P > .05$). The anesthesia time and length of stay in the operating room were significantly shorter in the R-S group than in the S-C-P group, although operation time was similar between the groups (all $P < .001$). The surgical rating score was significantly higher in the R-S group than in the S-C-P group ($P = .001$) (Table III).

There was no clinical evidence of residual neuromuscular blockade or neuromuscular blockade recurrence in either group.

DISCUSSION

To the best of our knowledge, this is the first study to compare the effects of different muscle relaxant/reversal agent regimens in patients undergoing LMS. The present study demonstrates that the R-S regimen results in a better surgical condition and shorter anesthesia time than the S-C-P regimen.

Our results show that the R-S regimen resulted in higher surgical rating scores than the S-C-P regimen. The LMS five-point surgical rating scale (Table I) used in the current study was created with an experienced surgeon who participated in our study and was based on the quality of the working conditions while also considering exposure of the surgical site and the degree of muscle relaxation. In the R-S group, no patient required additional NMBAs, whereas 50% of patients in the S-C-P group received additional doses. This suggests that the R-S regimen offers a sufficiently deep neuromuscular blockade and improves surgical conditions.

The nondepolarizing NMBA, rocuronium, has been studied as an alternative to succinylcholine,[13,14] because of the complications associated with succinylcholine, such as hyperkalemia, myoglobulinemia, and myalgia, as well as increased gastric, intracranial, and

TABLE III.
Intraoperative Data.

Variable	S-C-P Group, n = 40	R-S Group, n = 40	P
Addition of neuromuscular blocking agents, no.	20*	0	<.001
Recovery of T1 to 10%, s	190 (105–300)	271 (183–330)	.082
Recovery of T1 to 90%, s	240 (180–390)	377 (334–435)	.086
Time to first spontaneous breath, s	240 (70–325)	263 (175–334)	.343
Time to eye opening, s	300 (180–420)	340 (200–517)	.095
Time to extubation, s	380 (286–495)	430 (366–510)	.156
Anesthesia time, min	35.2 ± 7.0*	28.4 ± 7.5	<.001
Length of stay in the operating room	38.6 ± 7.5*	31.0 ± 7.7	<.001
Surgical rating score	5.0 (4.0–5.0)†	5.0 (5.0–5.0)	.001

Values are reported as median (interquartile range), mean ± standard deviation, or number of patients.
*$P < .001$, S-C-P group compared with R-S group.
†$P < .05$, S-C-P group compared with R-S group.
R-S = rocuronium-sugammadex; S-C-P = succinylcholine-cisatracurium-pyridostigmine.

intraocular pressures.[4,5] Rocuronium (0.6–1.2 mg/kg) typically produces complete neuromuscular block within 2 minutes, as compared with an average of 1 minute with 1 mg/kg succinylcholine.[15,16] We used higher doses of rocuronium (1 mg/kg) during anesthetic induction in the R-S group, as rapid and intensive neuromuscular block is required in LMS. Because the duration of LMS is short (~12–14 minutes in our study), a higher dose of sugammadex is required for rapid recovery of neuromuscular function to reverse the deep neuromuscular block.[11] It has been reported that 4 to 16 mg/kg sugammadex is ideal for rapid recovery from deep or profound neuromuscular blockade.[17,18] High-dose (1.2 mg/kg) rocuronium-induced neuromuscular blockade with 16 mg/kg sugammadex is achieved significantly faster than spontaneous recovery from 1 mg/kg succinylcholine.[7] However, we used 2 mg/kg sugammadex in the current study. The main reason regarding the reduced dose of sugammadex used in this study was its cost. The cost of 200 mg of sugammadex (one vial) in the Republic of Korea is approximately US$210, which is 200 times higher than the cost of pyridostigmine. In an average patient (67 kg in our study), the cost of sugammadex is US$200 for 2 mg/kg, US$400 for 4 mg/kg, and US$800 for 16 mg/kg. Because of this high price, we tried to use one vial of sugammadex. Furthermore, the total hospital cost is less than US$1,000, because LMS is performed in an ambulatory setting. Patients may not accept the ~50% increase in hospital costs caused by the use of more than two vials of sugammadex. Therefore, we used a dose of 2 mg/kg sugammadex, which is reportedly sufficient to reverse moderate rocuronium-induced neuromuscular blockade,[19] considering the cost-effectiveness of sugammadex for reversal of high-dose rocuronium neuromuscular block.

It could be argued that it would have been better to compare the R-S regimen with continuous succinylcholine infusion to perform a more accurate comparison of rocuronium versus succinylcholine. Nevertheless, in the S-C-P group, we used a single bolus of succinylcholine with cisatracurium instead of continuous succinylcholine infusion. A single bolus injection of succinylcholine for anesthetic induction is not sufficient to maintain deep neuromuscular blockade throughout the entire operation. Therefore, to maintain intense paralysis, a continuous infusion of succinylcholine or small boluses of nondepolarizing NMBAs are normally used.[20] However, continuous succinylcholine infusion can increase the risk of phase II neuromuscular block even during short surgical procedures (less than 90 min).[21,22] Increased succinylcholine dose has also been reported to prolong the duration of abdominal fasciculation.[23] Other studies have reported the advantages of a reduced succinylcholine dose,[23,24] as it minimizes the incidence of malignant hyperthermia, myalgia, masseter spasm, rhabdomyolysis, and hyperkalemia.[9,25] We therefore decided to use a single bolus of succinylcholine with cisatracurium, a nondepolarizing NMBA with intermediate duration, instead of a continuous infusion of succinylcholine.

In the present study, the R-S regimen resulted in a shorter anesthesia time than the S-C-P regimen. Reduced anesthesia time also reduces the length of stay in the operating room and can facilitate rapid surgical turnover. It is advantageous in LMS, which has a short operation time and is performed in an ambulatory setting.[4] As expected, there was no significant difference in the time from administration of the reversal agent to recovery of the TOF ratio to 0.9 or extubation between groups. We could not reduce the time required for reversing the neuromuscular block, possibly due to the low dose of sugammadex that was used for reversal in the current study (2 mg/kg). Although there was no significant difference between groups in the time from administration of the reversal agent to recovery of neuromuscular blockade, the anesthesia time was significantly shorter in the R-S group compared to the S-C-P group. This difference is because the time from the end of the operation to the appearance of T2 was added to the anesthesia time in the S-C-P group. We administered sugammadex to the patients in the R-S group immediately after the operation, which resulted in the shorter anesthesia time in this group. However, in the S-C-P group, the reversal agent was administered at the appearance of the T2 on the TOF that revealed a moderate neuromuscular blockade. The time from the end of the operation to administration of reversal agent was 250 ± 183 seconds in the S-C-P group (data not shown), which prolonged the recovery time and resulted in a longer anesthesia time in this group.

In this study, we discussed the anesthetic method and the use of NMBAs and reversal agents with the surgeon at the beginning of the study. The surgeon was fully aware of the side effects of the anesthetics and potential drug-drug interactions. Aminoglycoside antibiotics may increase the blood levels of succinylcholine or cisatracurium, resulting in an increase in the risk of related adverse events.[26] In addition, sugammadex may reduce the blood levels and effects of hormonal contraceptives, and increase the risk of breakthrough bleeding.[27] Therefore, we excluded from the analysis patients receiving antibiotics such as amikacin or tobramycin and hormonal contraceptives such as estradiol, norethindrone, and levonorgestrel.

Our study has a limitation. The surgical rating score was assessed on the basis of the degree of larynx exposure. This was influenced not only by neuromuscular relaxation but also by anatomical factors. Although we excluded patients who were expected to have difficult tracheal intubations owing to anatomical factors, the possibility remains that some patients with anatomical factors contributing to a lower surgical rating scale were missed. Therefore, further studies are required that assess surgical conditions while also considering patient anatomical factors and the degree of neuromuscular relaxation.

CONCLUSION

The R-S regimen of 1 mg/kg rocuronium and 2 mg/kg sugammadex provided better surgical conditions and shorter anesthesia time compared to the S-C-P regimen of 1 mg/kg succinylcholine, 0.08 mg/kg cisatracurium,

and 0.2 mg/kg pyridostigmine. Therefore, we conclude that the R-S regimen is superior to the S-C-P regimen as an NMBA/reversal agent combination in patients undergoing ambulatory LMS. Furthermore, the results of this study are thought to be useful for any type of short-duration microlaryngeal surgery, not just LMS.

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