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AIRWAY AND RESPIRATION

Deep neuromuscular block improves the surgical conditions for laryngeal microsurgery

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Abstract

Background: Adequate neuromuscular block is required throughout laryngeal microsurgery. We hypothesized that the surgical conditions would improve under a deeper level of rocuronium-induced neuromuscular block.

Methods: Seventy-two patients undergoing laryngeal microsurgery were randomly allocated to either the 'post-tetanic counts 1-2' (PTC1-2) group or the 'train-of-four counts 1-2' (TOFcount1-2) group according to the level of neuromuscular block used. Two different doses of rocuronium (1.2 or 0.5 mg kg^{-1}) were used after anaesthetic induction, and two respective targets of neuromuscular block (post-tetanic counts ≤2 or train-of-four count of 1 or 2) were used. Surgical conditions were assessed by the surgeon using a five-point rating scale (extremely poor/poor/acceptable/good/optimal), and clinically acceptable surgical conditions were defined as those which were rated acceptable, good, or optimal. The occurrence of vocal cord movement and postoperative adverse events was assessed.

Results: The surgical conditions were significantly different between the PTC1-2 and TOFcount1-2 groups (extremely poor/poor/acceptable/good/optimal: 0/2/1/7/26 and 3/10/2/14/7, respectively, $P<0.001$). The incidence of clinically acceptable surgical conditions was significantly higher in the PTC1-2 group than in the TOFcount1-2 group (94 *vs* 64%, $P=0.003$). The percentage of patients who exhibited vocal cord movement was significantly lower in the PTC1-2 group than in the TOFcount1-2 group (3 *vs* 39%, $P<0.001$). The incidence of postoperative adverse events was not significantly different except for the less frequent occurrence of mouth dryness in the PTC1-2 group ($P=0.035$).

Conclusions: Deep neuromuscular block (post-tetanic count of 1-2) surgical conditions in patients undergoing laryngeal microsurgery improves.

Clinical trial registration: NCT01980069.

Key words: larynx; neuromuscular blockade; neuromuscular monitoring

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Adequate muscle relaxation is required throughout laryngeal microsurgery because the larynx must be directly visualized using a rigid laryngoscope. The laryngeal muscle requires deep neuromuscular block (NMB) because it is more resistant to neuromuscular blocking agents than other muscles.[1][2] Moreover, unexpected intraoperative patient movements and laryngeal responses can provoke cardiovascular instability and respiratory compromise.[3] Therefore, during laryngeal microsurgery, the

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maintenance of deep NMB until the end of surgery appears to be desirable for achieving clear and quiet laryngoscopic conditions.

However, the maintenance of deep NMB during surgery is likely to lead to postoperative residual muscle relaxation, which has been reported to occur in 33–64% of patients after admission to the recovery room. Additionally, postoperative residual muscle relaxation contributes to the occurrence of pulmonary complications, such as airway obstruction, aspiration, and hypoxia, and of delayed discharge.[4–6] The risk of residual muscle relaxation inevitably increases after laryngeal microsurgery, because most procedures are completed in less than 30 min, which does not allow the patient time to spontaneously recover from the muscle relaxation, before an acetylcholinesterase inhibitor is used. Therefore, in clinical practice, a single reduced dose of an intermediate-acting, non-depolarizing neuromuscular blocking agent is typically administered at the time of anaesthetic induction to facilitate rapid recovery of the protective airway reflexes and to prevent delayed discharge, even though moderate NMB is not ideal for laryngeal microsurgery.[1 3] However, previous reports have demonstrated that the maintenance of deep NMB during laparoscopic surgery, including cholecystectomy, hysterectomy, and prostatectomy, provided better surgical conditions than moderate NMB[7–11] and that the risk of delayed discharge as a result of deep NMB was avoided using sugammadex.[12–15] However, to the best of our knowledge, no study has evaluated the effect of deep NMB on surgical conditions during laryngeal microsurgery.

Therefore, based on the hypothesis that deep NMB would improve the surgical conditions during laryngeal microsurgery, we compared the effect of deep NMB with that of moderate NMB on surgical conditions during laryngeal microsurgery.

Methods

This prospective, randomized study was approved by the Institutional Review Board of Severance Hospital (ref: 4-2013-0451) in Seoul, Republic of Korea, and was registered at ClinicalTrials.gov (ref: NCT01980069, November 1, 2013). Written informed consent was obtained from all patients. The participants included adults aged 20–80 yr who exhibited an ASA physical status of I, II or III and were undergoing elective laryngeal microsurgery requiring tracheal intubation under general anaesthesia. Patients with a known neuromuscular disease, a history of difficult intubation, cervical spine injury or pathology, acute or chronic renal failure, liver cirrhosis, liver failure, or an allergic reaction to non-depolarizing neuromuscular blocking agents were excluded.

The patients were randomly assigned to two groups using a computer-generated randomization table: the 'post-tetanic counts 1-2' (PTC1-2) group or the 'train-of-four counts 1-2' (TOF-count1-2) group. The dose of rocuronium administered at anaesthesia induction, the degree of intraoperative NMB, and the

selection of drugs for NMB antagonism differed according to the group assignment.

Preoperative airway assessments, including the modified Mallampati classification, the thyromental distance, and the interincisor gap, were conducted before anaesthesia induction by one of the investigators (H.J.K.), who was unaware of the group assignment. A bispectral index sensor (BIS™ sensor; Covidien, Boulder, CO, USA) was attached to the patient's forehead. Two electrodes were placed on the skin above the ulnar nerve and were connected to an acceleromyograph (TOF-Watch® SX, Roganon Ireland Ltd., a subsidiary of Merck and Co., Swords, Co. Dublin, Ireland).

Propofol and remifentanil were administered via continuous i.v. infusion. After loss of consciousness was confirmed, neuromuscular activity monitoring via acceleromyography was initiated. The acceleromyograph was calibrated with 50 Hz tetanic stimulation for 5 s and train-of-four (TOF) stimulation for 3 min.[12 13] The ulnar nerve was stimulated, and the movement of the adductor pollicis muscle was monitored. After the calibration was completed, repetitive TOF stimulation was initiated. Rocuronium was administered intravenously at the dose determined by the group assignment (1.2 mg kg^{-1} for the PTC1-2 group or 0.5 mg kg^{-1} for the TOFcount1-2 group). Tracheal intubation was performed after a TOF count of 0 was confirmed by a single anaesthetist (B.R.L.), who was unaware of the group assignment. The Cormack and Lehane grade of the laryngeal view was recorded.[16] Anaesthesia was maintained via continuous i.v. infusion of propofol and remifentanil, targeting a bispectral index of 40–60. Neuromuscular activity monitoring was performed repeatedly using TOF stimulation or post-tetanic count (PTC) stimulation, until the TOF ratio was greater than 0.9. TOF stimulation and PTC stimulation were repeated every 15 s and two min, respectively. PTC stimulation at 1 Hz for 15 s was performed three s after tetanic stimulation at 50 Hz for five s.[17] Additional rocuronium was administered intravenously according to the group assignment. Rocuronium 0.15 mg kg^{-1} was administered to maintain the PTC at less than two or the TOF count at one or two based on acceleromyography in the PTC1-2 group and the TOFcount1-2 group, respectively. Additionally, if the surgeon asked the anaesthetist for deeper NMB to achieve an adequate surgical field, rocuronium 0.15 mg kg^{-1} was administered. The peripheral temperature was measured continuously at the axilla on the same side as neuromuscular activity was monitored, with the shoulder completely adducted and at a constant temperature of 35°C or greater using a forced air warmer.[18]

At the end of surgery, the degree of NMB was assessed using TOF stimulation. If the TOF response was absent, the PTC was observed. Patients received either sugammadex (Bridion®, Merck Sharp and Dohme (MSD), Oss, The Netherlands) at different doses or neostigmine at 50 µg kg^{-1} according to their group assignment. Sugammadex at eight or four mg kg^{-1} was administered to patients in the PTC1-2 group if the PTC was ≤2 or >2, respectively. Neostigmine was administered with glycopyrrolate 10 µg kg^{-1} to the TOFcount1-2 group if a second twitch appeared upon TOF stimulation. Anaesthesia was maintained until the TOF ratio recovered to 0.9.

The surgeon (W.S.K.), who was blinded to the group assignment, performed the laryngeal microsurgery. The surgeon evaluated the resistance of the rigid laryngoscope, the movement of the vocal cords, and the position of the vocal cords, immediately upon the placement of the rigid laryngoscope, to expose the vocal cords. The surgeon also scored the difficulty of exposing the vocal cords using a rigid laryngoscope, using a three-point scale: difficult, acceptable, or easy. The duration of vocal cord exposure was recorded from the insertion of the rigid laryngoscope into the patient's mouth to the fixation of suspension. The surgeon

observed the movement of the vocal cords during surgery, and the number of vocal cord movements was recorded. After the surgery was completed, the surgeon subjectively evaluated the surgical conditions using a five-point surgical rating scale: extremely poor conditions, poor conditions, acceptable conditions, good conditions, or optimal conditions. The occurrence of coughing and movement by the patient during the surgery was recorded.

Tracheal extubation was performed when a TOF ratio of 0.9 and spontaneous ventilation were observed. The patient was then transferred to the post-anaesthesia recovery room. The investigator (B.R.L.), who was blinded to the group assignment, evaluated the occurrence of postoperative complications including nausea, vomiting, sore throat, and mouth dryness within 15 min after the patient's arrival at the post-anaesthesia recovery room.[19] Nausea, sore throat and mouth dryness were classified using a four-point scale: none, mild, moderate, or severe. The level of consciousness was also assessed and classified using a three-point scale: awake and oriented, arousable with minimal stimulation, or responsive only to tactile stimulation.[19]

The operation and anaesthesia times were recorded. The time from the end of surgery to the recovery of a TOF ratio of 0.9 and the time from the end of surgery to discharge from the operating room to the recovery room were recorded. The mean bp and heart rate were recorded at five time points: before anaesthesia induction (baseline), before the injection of sugammadex or neostigmine, five min after the injection of sugammadex or neostigmine, immediately after tracheal extubation, and after arrival at the post-anaesthesia recovery room.

Statistical analysis

The primary outcome was the percentage of patients with clinically acceptable surgical conditions according to the surgeon's perspective. Clinically acceptable surgical conditions were those which the surgeon rated as acceptable, good, or optimal. The secondary outcomes were the time from the end of surgery

to discharge from the operating room to the recovery room, the difficulty of exposing the vocal cords, intraoperative haemodynamics, and postoperative adverse events. The sample size needed to detect a 25% difference in the primary outcome measure between the PTC1-2 and TOFcount1-2 groups was determined. A minimum of 72 patients was estimated to be required based on a type one error of 0.05 and a power of 0.8 assuming that the primary outcomes of the PTC1-2 and TOFcount1-2 groups were 99% and 74%, respectively. ASAphysical status, Cormack-Lehane grade, laryngoscope resistance, vocal cord movement, vocal cord position, difficulty of exposing the vocal cords, surgical conditions, patient coughing, patient movement, level of consciousness and postoperative adverse events were compared using Fisher's exact test. Gender, Mallampati classification and vocal cord movement were compared using the χ^2 test. Weight, height, age, the thyromental distance, the interincisor gap, the anaesthesia time, the operation time, the duration of vocal cord exposure, the number of vocal cord movements, the time from the end of surgery to the recovery of a TOF ratio of 0.9 and the time from the end of surgery to discharge from the operating room to the recovery room, were compared using the Mann-Whitney U-test. Mean arterial pressure and heart rate were compared between the PTC1-2 and TOFcount1-2 groups, using repeated measures analysis of variance (RMANOVA). Values are presented as means (SD) (range) or number of patients (%). SAS software (version 9.2, SAS Institute, Inc., Cary, NC, USA) was used for the statistical analysis. The results were considered to be statistically significant if the P value was <0.05.

Results

The study enrolled 72 patients (Fig. 1). The patient characteristics, airway assessments, and anaesthesia duration were not significantly different between the PTC1-2 and TOFcount1-2 groups (Table 1). The doses of neostigmine and sugammadex used were 3.4 (0.9) and 314 (121) mg, respectively.
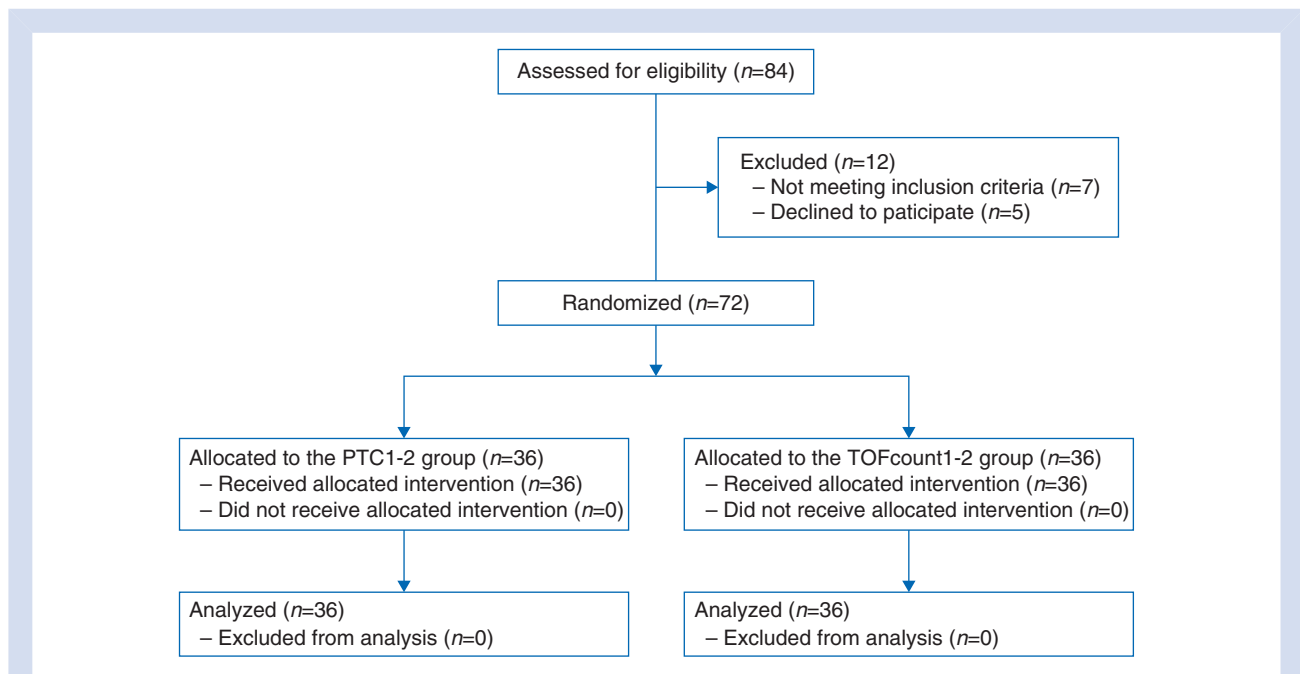

Fig 1 Study flow diagram.

The resistance of the rigid laryngoscope was significantly lower in the PTC1-2 group than in the TOFcount1-2 group (Table 2). Vocal cord movement was observed only in the TOFcount1-2 group, although there was no significant difference in vocal cord movement between the two groups. In all patients in the PTC1-2 group, the vocal cords were abducted. The difficulty of exposing the vocal cords was significantly lower in the PTC1-2 group than in the TOFcount1-2 group. The duration of vocal cord exposure was comparable between the two groups. The incidence and number of vocal cord movements during surgery were significantly lower in the PTC1-2 group than in the TOFcount1-2 group.

The incidence of clinically acceptable surgical conditions was significantly higher in the PTC1-2 group than in the TOFcount1-2 group (Table 2). Coughing and movement were observed only in the TOFcount1-2 group, although there was no significant difference in these variables between the two groups. Additional

rocuronium was administered to two patients in the TOFcount1-2 group and to one patient in the PTC1-2 group.

The changes in mean bp and heart rate during the perioperative period were not significantly different between the two groups. The time from the end of the operation to the recovery of a TOF ratio of 0.9 was significantly shorter in the PTC1-2 group, than in the TOFcount1-2 group [4.8 (2.6) min and 18.2 (14.9) min, respectively, P<0.001]. The time from the end of the operation to discharge from the operating room to the recovery room was significantly shorter in the PTC1-2 group, than in the TOFcount1-2 group [15.1 (7.0) min and 24.9 (13.9) min, respectively, P<0.001]. Mental status, nausea, vomiting, and sore throat after surgery were not significantly different between the two groups. Mouth dryness after surgery was significantly more severe in the TOFcount1-2 group, than in the PTC1-2 group (none/mild/moderate/severe: 25/7/2/2 and 33/1/2/0, respectively, P=0.035).

Table 1 Patient characteristics and airway assessments. The data are presented as the means (range or sD) or the numbers of patients. PTC1-2: deep neuromuscular block group exhibiting a post-tetanic count of 1-2; TOFcount1-2: moderate neuromuscular block group exhibiting a train-of-four count of 1-2

	PTC1-2 (n=36)	TOFcount1-2 (n=36)
Male/female	23/13	23/13
Age (yr)	55 (27–75)	51 (21–70)
Weight (kg)	63 (9)	68 (18)
Height (cm)	165 (9)	163 (19)
ASA physical status (I,II, III)	27/7/2	29/6/1
Mallampati classification (1/2/3/4)	3/16/17/0	10/16/10/0
Thyromental distance (cm)	7.2 (1.1)	7.5 (1.3)
Interincisor gap (cm)	4.2 (0.7)	4.3 (0.9)
Anaesthetic time (min)	44.1 (16.8)	49.1 (19.6)
Operation time (min)	13.3 (11.4)	9.0 (11.7)
Cormack and Lehane grade (1/2/3/4)	30/3/3/0	24/8/4/0

Discussion

The current study demonstrated that deep NMB (PTC 1-2) during laryngeal microsurgery significantly improved surgical conditions compared with moderate NMB (TOF count 1-2).

In laryngeal microsurgery, deep NMB is thought to be necessary for exposing the larynx and performing the surgery.[3] This is because the laryngeal muscles are more resistant to neuromuscular blocking agents than peripheral muscles, such as the adductor pollicis muscle, because of the greater acetylcholine receptor density in fast-twitch muscles.[20 21] A previous report demonstrated that the maximum NMB was less in laryngeal adductor muscles than in the adductor pollicis muscle, after the administration of the same dose of 0.6 mg kg^{-1} rocuronium.[22] In our study, the surgeon experienced lower laryngoscope resistance and easier vocal cord exposure in the PTC1-2 group than in the TOFcount1-2 group. This result suggests that deep NMB might help to reduce repeated attempts at laryngoscope insertion or vocal cord exposure using excessive force, which can result in inadvertent trauma to the pharyngeal mucosa or teeth, imperfect resection, and abandonment of the procedure, especially among surgeons with limited experience.[23 24] Moreover, the laryngeal muscle recovers more rapidly from muscle relaxation than the peripheral muscles.[20] Therefore, the laryngeal muscle may have partially

Table 2 Association of the surgical conditions with subjective and objective, including ease of vocal cord exposure, intraoperative vocal cord movement, overall surgical conditions, and the occurrence of coughing and movement. The data are presented as the means (sD) (range) or the numbers of patients. PTC1-2: deep neuromuscular block group exhibiting a post-tetanic count of 1-2; TOFcount1-2: moderate neuromuscular block group exhibiting a train-of-four count of 1-2

	PTC1-2 (n=36)	TOFcount1-2 (n=36)	P-value
Vocal cord exposure by the surgeon			
Laryngoscope resistance (none/slight resistance/active resistance)	27/9/0	19/12/5	0.026
Vocal cord movement (none/moving)	36/0	34/2	0.493
Position of the vocal cords (abducted/intermediate/closed)	36/0/0	34/2/0	0.493
Difficulty in exposing the vocal cords (difficult/acceptable /easy)	7/7/22	15/10/11	0.029
Duration of vocal cord exposure (sec)	39 (15)	42 (21)	0.905
Intraoperative vocal cord movement			
Occurrence of vocal cord movement (no/yes)	35/1	22/14	<0.001
Number of vocal cord movements	0.2 (1.0) (0–6)	1.6 (2.7) (0–10)	<0.001
Overall surgical conditions			
Surgical conditions (extremely poor/poor/acceptable/good/optimal)	0/2/1/7/26	3/10/2/14/7	<0.001
Clinically acceptable surgical conditions (yes/no)	34/2	23/13	0.003
Coughing during surgery	0	3	0.239
Movement during surgery	0	2	0.493

recovered from NMB even when the adductor pollicis muscle shows no TOF response, and this is the reason deep NMB may be required to eliminate unexpected laryngeal reactions to surgical stimuli. In our study, the vocal cords moved less frequently during surgery, resulting in a more stable surgical field, in PTC1-2 group than in the TOFcount1-2 group. Coughing and movement during surgery, which can cause haemodynamic instability or unintended trauma,[3] were observed in three and two patients in the TOFcount1-2 group, respectively, but in no patients in the PTC1-2 group. Similarly, a previous report recommended that a neuromuscular blocking agent be used to obtain optimal vocal cord conditions, lacking reactions to stimuli during tracheal intubation.[25] Therefore, according to the results of our study, the maintenance of deep NMB during laryngeal microsurgery appears to provide better surgical conditions, including the abolishment of intraoperative vocal cord movement. Our results correspond with previous reports showing that the use of deep NMB during laparoscopic surgery provided superior surgical conditions to moderate NMB,[7–11] because under moderate NMB, the diaphragm and abdominal muscles, similar to the laryngeal muscles, were not fully relaxed, causing hiccups or coughing.[26]

In the present study, we used different types of neuromuscular antagonism agents between the two groups (sugammadex in the PTC1-2 group and neostigmine in the TOFcount1-2 group), similar to the methods used in previous reports.[9 11] We chose different neuromuscular antagonism agents for each group because it is clear that using neostigmine in the PTC1-2 group would require a longer neuromuscular recovery time (mean of 50.4 min under sevoflurane anaesthesia based on a previous report[12]), to achieve sufficient recovery of muscle function, as determined by a TOF ratio ≥0.9 for the adductor pollicis muscle,[13 27 28] despite a generally very short duration of laryngeal microsurgery (mean of 13.3 and 9 min in the PTC1-2 and TOFcount1-2 groups, respectively, in the present study). In addition, the primary outcome (surgical conditions) was not affected by the use of different neuromuscular antagonism agents but rather by different degrees of intraoperative NMB. Therefore, we decided to use sugammadex in the PTC1-2 group to prevent residual relaxation and delayed discharge from the operating room and to use neostigmine in the TOFcount1-2 group to reflect our current practice.

The number of postoperative adverse events did not significantly differ between the PTC1-2 and TOFcount1-2 groups except for the degree of mouth dryness, which might be a side-effect of anticholinergic drugs such as glycopyrrolate, which was co-administered with neostigmine, as demonstrated in previous reports.[19 29] Although anticholinergic drugs can cause other adverse effects, such as tachycardia,[29] there was no significant difference in heart rate between the two groups in our study.

Postoperative sore throat is a common complication after laryngeal microsurgery.[30 31] This complication is induced by laryngeal injuries that occur during tracheal intubation and surgery.[31] In our study, the quality of tracheal intubation might be similar for all patients, because a single anaesthetist performed the tracheal intubations after achieving a TOF count of 0 and because the preoperative airway assessments and Cormack and Lehane grades of the laryngeal view were not significantly different between the two groups.[25] However, in laryngeal microsurgery, postoperative sore throat was reported to be associated with greater pressure exerted on the tongue and the laryngopharynx during surgery, or a longer surgery duration (more than 30 min).[31] Therefore, we expected that the incidence of postoperative sore throat would be greater in the TOFcount1-2 group than in the PTC1-2 group because the laryngoscope resistance and the difficulty of exposing the vocal cords were

significantly greater in the TOFcount1-2 group than in the PTC1-2 group. However, there was no significant difference in the incidence of postoperative sore throat between the two groups. We believe that the direct trauma to the larynx during surgery was sufficiently intensive to mask the possible favourable effect of deep NMB on postoperative sore throat. Moreover, the very short duration of surgery, which was similar between the two groups, may have contributed to this finding.

The present study has several limitations. First, the anaesthetist who maintained the anaesthesia could not be blinded to the group assignment, because of the different levels of NMB used during surgery. However, tracheal intubation was performed by a single anaesthetist who was unaware of the group assignment, and there was no significant difference in the Cormack-Lehane grades, which reflect the difficulty of tracheal intubation. In addition, the surgeon who evaluated the surgical conditions, which served as the primary outcome of this study, was also blinded to the group assignment. Therefore, the improvement in the surgical conditions was most likely as a result of the achievement of a deeper level of NMB, as reflected by the absence of patient coughing, movement, and vocal cord movement. Second, we used four or eight mg kg^{-1} sugammadex according to the degree of NMB at the time of antagonism. This dose is not consistent with the manufacturer's guidelines. We chose eight mg kg^{-1} sugammadex based on the protocol of a previous report evaluating deep NMB[8] or a dose-finding study that demonstrated that eight mg kg^{-1} sugammadex reduced the time to recovery from deep NMB (PTC 1-2) by 50%, compared with four mg kg^{-1} sugammadex.[13] Third, we developed a novel scale to evaluate the surgical conditions during laryngeal microsurgery via a thorough discussion with the surgeon. This scale was used to assess the effect of deep NMB on the surgical conditions during laparoscopic surgery.[11] This tool has not been validated in other studies; however, in this study, one surgeon, who was blinded to the group assignments performed the laryngeal microsurgery; this study design reduced the variability in the assessment of the surgical conditions. Additionally, we observed other objective parameters, such as vocal cord movement to compensate for the limitations of using subjective scales.

In summary, deep NMB improved the surgical conditions compared with moderate NMB in patients undergoing laryngeal microsurgery.

Authors' contributions

Study design/planning: H.J.K., K.L., W.K.P., W.S.K., Y.C.Y.
Study conduct:H.J.K., B.R.L., H.M.J., Y.W.K., Y.W.S., W.S.K.
Data analysis: H.J.K., K.L., W.K.P., H.M.J.
Writing paper: H.J.K., Y.C.Y.
Revising paper: all authors

Declaration of interest

None declared.

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