The effects of deep neuromuscular blockade during robot-assisted transaxillary thyroidectomy on postoperative pain and sensory change; prospective randomized controlled trial

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Directed by Professor Young Chul Yoo

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ABSTRACT

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Background

The occurrence of significant pain and paresthesia after robot-assisted transaxillary thyroidectomy has been reported, and some patients experience chronic symptoms even three months after surgery. Assuming that complete muscle relaxation could reduce the retractor pressure required for chest skin flap elevation, deep neuromuscular block may help reduce postoperative pain and sensory changes. This study scrutinized the effects of deep neuromuscular block during robot-assisted transaxillary thyroidectomy on postoperative pain and sensory changes.

Method

In this single-blinded, prospective, randomized controlled trial, eighty-eight patients who underwent robot-assisted transaxillary thyroidectomy were enrolled and randomly allocated to either the moderate neuromuscular block group or the deep neuromuscular block group. Study endpoints included postoperative pain, paresthesia, and sensory change after surgery.

Results

The linear mixed models for numeric rating scale pain scores in the chest, neck, and axilla all showed significant intergroup differences over time ($p = 0.003$ in the chest; $p = 0.001$ in the neck; $p = 0.002$ in the axilla). In the post hoc analysis, the pain scores of the chest, neck, and axilla were significantly lower in the deep neuromuscular block group on postoperative day one compared to the moderate neuromuscular block group. (3.6 vs. 1.6 in chest, adjusted $p < 0.001$; 3.3 vs. 1.4 in neck, adjusted $p < 0.001$; 4.0 vs. 2.4 in axilla, adjusted $p < 0.001$)

Conclusion

This study demonstrated that deep neuromuscular block could reduce postoperative pain after robot-assisted transaxillary thyroidectomy. However, it could not demonstrate that deep neuromuscular block reduces paresthesia or hypoesthesia after the surgery.

Key words : robot-assisted transaxillary thyroidectomy; robot-assisted endoscopic thyroidectomy, deep neuromuscular block, postoperative pain

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I. INTRODUCTION

Robot-assisted transaxillary thyroidectomy (RATT) has gained popularity in recent years and offers many advantages over conventional open surgery, including improved cosmetic satisfaction without any difference in cancer control or safety.[1-3] However, several studies have reported the occurrence of significant pain and paresthesia after RATT, and some patients experience chronic symptoms even three months after surgery.[4-7] Many studies have attempted to mitigate the postoperative pain and sensory changes, but a definitive solution has not yet been found.

The surgical procedure for RATT includes chest skin flap elevation using an external retractor system to make a working space.[6,8,9] (Fig. 1) During this procedure, significant pressure is applied to the skin flap, and this pressure is presumably associated with postoperative pain and sensory changes.[5,10] Assuming that complete muscle relaxation could enhance visualization and reduce the retractor pressure required for skin flap elevation, deep neuromuscular block (NMB) may help reduce postoperative pain and

sensory changes. In laparoscopic abdominal surgery, deep NMB has been demonstrated to mitigate postoperative pain and improve surgical conditions.[11-13] Nevertheless, its effect on RATT remains unknown. Therefore, we scrutinized the effect of deep NMB during RATT on postoperative pain and sensory changes.

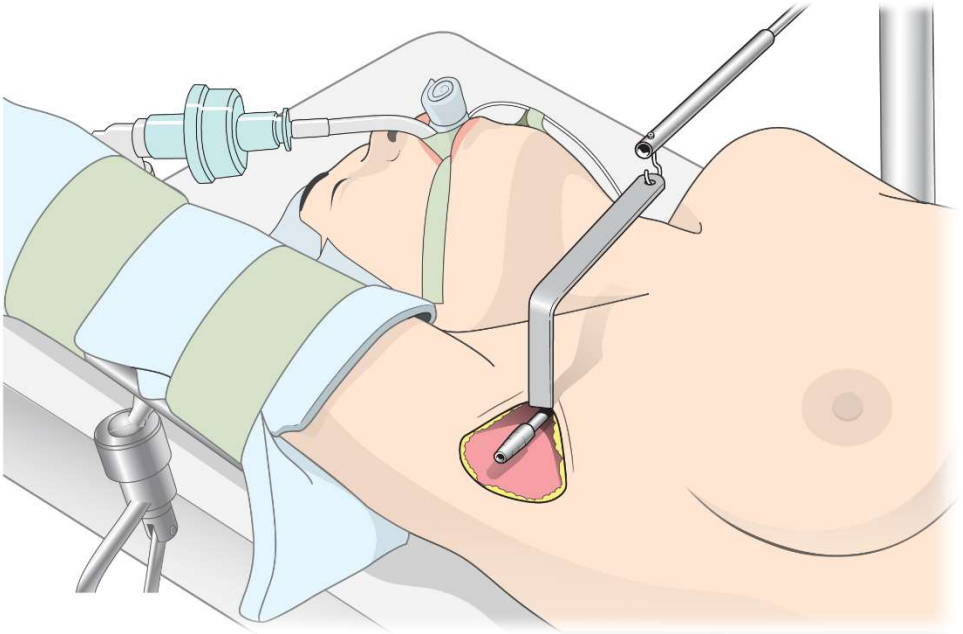

Figure 1. Description of chest skin flap elevation in robot-assisted transaxillary thyroidectomy.

II. MATERIALS AND METHODS

1. Patient enrollment and randomization

This study was designed as a single-blinded, prospective, randomized controlled trial. The Institutional Review Board and Hospital Research Ethics Committee of the Severance Hospital at Yonsei University College of Medicine approved this study on 27 November 2018 (#4-2018-0963). It was registered at ClinicalTrials.gov (NCT03871387) on 12 March 2019. We obtained written informed consent from all participants.

We included patients aged 20–70 years who underwent RATT and had an American Society of Anesthesiologists physical status of I–III. The following patients were excluded: (1) patients scheduled for radical neck node dissection; (2) those undergoing simultaneous surgeries for other organs; (3) those with other accompanying cancers; (4) those with a BMI > 30 kg/m^2; (5) pregnant or lactating woman; (6) those with a history of liver or renal failure; (7) those with a history of allergic reaction to rocuronium or sugammadex; (8) those who already had chronic pain or paresthesia; (9) those who could not understand the consent form, such as people with low levels of literacy or foreigners.

The enrolled patients were randomly allocated to the moderate NMB group or the deep NMB group. Group allocation was performed by a predetermined randomization sequence, which was made by a computer-generated random table without any block or stratification. The random sequence was kept enclosed in an envelope. A predetermined investigator was responsible for random sequence security and group assignment, and that investigator did not participate in the subsequent research process. The patients, surgeons, and investigators who evaluated the outcomes were blinded to the group allocation. However, assignment results were disclosed to the attending anesthesiologists to control the level of NMB

according to groups.

2. Perioperative management and study protocol

When the patient arrived in the operation room, non-invasive blood pressure, electrocardiography, pulse oximetry, and bispectral index (BIS, Covidien, Dublin, Ireland) monitoring were initiated. A TOF-Watch® SX (Organon Ltd., Dublin, Ireland) was attached to the patient's wrist. Glycopyrrolate 0.1 mg was administered intravenously before induction. Continuous remifentanil infusion was initiated at a rate of 0.05 to 0.2 μg/kg/min, and 1.5 to 2 mg/kg of propofol was administered intravenously. The TOF-Watch® SX was calibrated when the patient became unconscious. After calibrating the device, 0.6 mg/kg of rocuronium was administered to the patient, and endotracheal intubation was performed. Anesthesia was maintained with desflurane and a continuous infusion of remifentanil. All surgeries were performed by three experienced surgeons (K.H. Nam, S.W. Kang, and C.R. Lee) who were blinded to the group allocation.

Rocuronium was continuously infused during surgery, and the infusion rate was adjusted differently for each group. For the moderate NMB group, the rate of rocuronium infusion was adjusted to maintain one to two responses in the train-of-four (TOF). For the deep NMB group, the infusion rate was adjusted to maintain zero responses in the TOF and one to two responses in the post-tetanic count.[14] The TOF-Watch® SX on the patient's wrist was used to monitor the TOF and post-tetanic count.[15] The attending anesthesiologists had been previously trained for controlling the level of NMB during surgery.

Before the end of the surgery, 1 g of propacetamol and 0.075 mg of palonosetron were administered. When the surgery was completed, sugammadex was administered intravenously (2 mg/kg for patients showing two or more TOF responses, and 4 mg/kg for

those showing fewer than two TOF responses), and the investigator measured the time from sugammadex injection to a TOF ratio of 0.9. After measuring the time, desflurane and remifentanil were discontinued, and the endotracheal tube was removed when spontaneous respiration recovered. Patients who complained of pain at the post-anesthesia care unit (PACU) were administered 50 mg of tramadol, and those who complained of nausea were administered 0.3 mg of ramosetron.

3. Study endpoints

The primary endpoint was the numeric rating scale (NRS) scores for pain on postoperative day (POD) 1. The secondary endpoints included (1) NRS scores for postoperative pain until three months after surgery, (2) postoperative paresthesia, (3) postoperative sensory changes, (4) postoperative nausea and vomiting, (5) time from sugammadex injection to TOF ratio of 0.9, and (6) postoperative complications.

Postoperative pain was evaluated using an NRS score of 0–10 (where 0 = no pain, and 10 = severe pain). The pain scores were separately evaluated for the neck, chest, and axilla, and were evaluated at PACU, POD 1, POD 3, and 3 months after surgery (POD 90). Paresthesia of the neck and chest was evaluated on a scale of 0–7 (where 0 = no paresthesia, and 7 = severe paresthesia) using a questionnaire on POD 1, POD 3, and POD 90.[16] Additionally, the degree of remnant sensation on the surgical site was evaluated using the pinprick test on POD 1, POD 3, and POD 90. For the pinprick test, the investigator pricked the patients' neck and chest on the surgical site with a 256 mN filament, and the patients were asked to rate the sensation in the pricked area as a percentage of the sensation on the opposite side of the chest (non-surgical site). Postoperative nausea and vomiting were assessed on a scale of 0–3 (where 0 = no nausea; 1 = mild nausea, that subsided without

medication; 2 = severe nausea requiring medication; and 3 = retching or vomiting) at PACU, POD 1, and POD 3.[17] All endpoint measurements were performed by investigators blinded to the group allocation.

4. Sample size and statistical analysis

A previous study reported a visual analogue scale pain score of 3.04 ± 1.28 on POD 1 after RATT.[18] Under the assumption that deep NMB could decrease the visual analogue scale score by 30%, the number of participants required to obtain a power of 90% was 44 in each group, considering a type 1 error (α) of 0.05 and a drop-out rate of 5%.

We used SAS software version 9.4 (SAS Inc., Cary, NC, USA) and IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. We performed the independent t-test or Mann–Whitney U test in comparing the continuous variables, and we conducted chi-square test or Fisher's exact test in comparing the categorical variables. The NRS pain score, paresthesia score, and degree of remnant sensation were analyzed using linear mixed models, and post hoc analysis was conducted with Bonferroni correction.

III. RESULTS

Eighty-eight patients were enrolled in the current study, and the patients were evenly allocated to the moderate NMB group (n = 44) or the deep NMB group (n = 44). Two cases of postoperative bleeding occurred in the deep NMB group; One of them underwent reoperation and was dropped from the study, and the other patient received only conservative management and was included in the analysis. Finally, eighty-seven patients were included in the analysis (Fig. 2). There was no missing value in the hospitalization data; however, data for POD 90 had missing values in 18 patients.

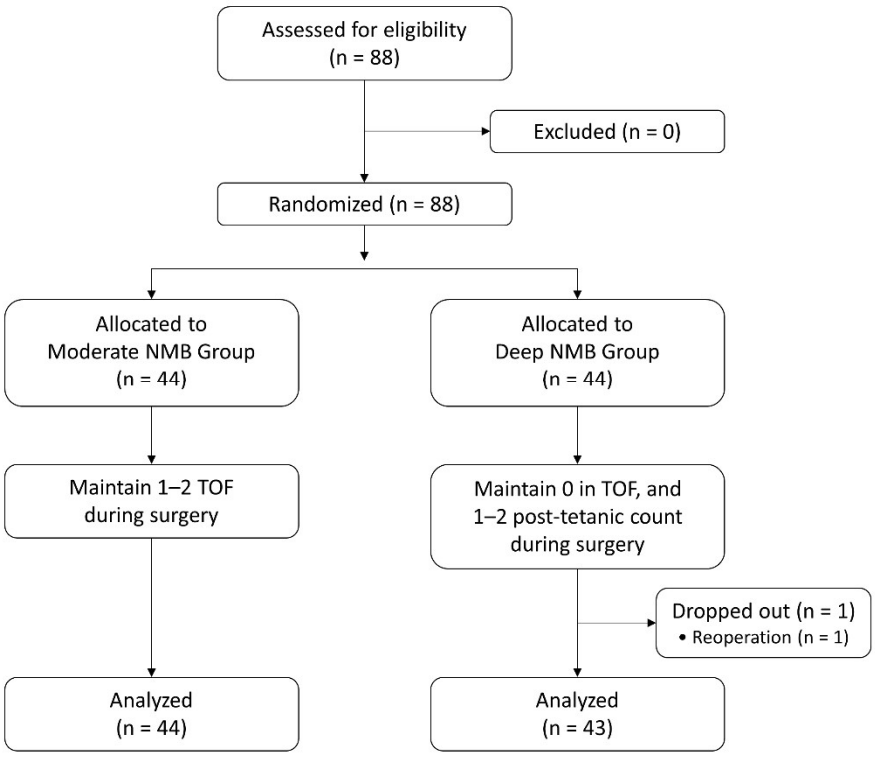

Figure 2. Flow diagram of the study. Abbreviations: NMB, neuromuscular block; TOF, train-of-four.

No significant intergroup differences were observed in demographic and clinical characteristics (Table 1). And there were no significant intergroup differences in operation type, surgeon, tumor size, and pathology result (Table 2). Rocuronium and sugammadex were administered in significantly larger doses in the deep NMB group than in the moderate NMB group (rocuronium, 57 vs. 110 mg, $p < 0.001$; sugammadex, 121 vs. 244 mg, $p < 0.001$). The vital signs and peak airway pressure did not show significant intergroup differences, except for the heat rate when the robot was undocked. The time from sugammadex injection to TOF ratio of 0.9 was significantly longer in the deep NMB group than in the moderate NMB group (99 vs. 147 sec, $p = 0.001$). No patients experienced respiratory failure or desaturation after surgery (Table 3).

Table 1. Baseline demographic and clinical characteristics

	Moderate NMB (n = 44)	Deep NMB (n = 43)	P-value
Sex (female)	41 (93.2)	40 (93.0)	> 0.999
Age (years)	36.3 ± 9.0	35.8 ± 9.1	0.795
BMI (kg/m^2)	22.9 ± 2.9	22.6 ± 3.4	0.663
ASA class			0.151
1	15 (34.1)	22 (51.2)	
2	25 (56.8)	20 (46.5)	
3	4 (9.1)	1 (2.3)	
Hypertension	0 (0)	1 (2.3)	0.494
DM	0 (0)	1 (2.3)	0.494
Old TB	0 (0)	1 (2.3)	0.494
HBV	1 (2.3)	1 (2.3)	> 0.999
Dyslipidemia	1 (2.3)	1 (2.3)	> 0.999
Asthma	3 (6.8)	1 (2.3)	0.616
HCD	3 (6.8)	2 (4.7)	> 0.999

Values are mean ± standard deviation, or number of patients (%). Abbreviations: NMB, neuromuscular block; ASA, American Society of Anesthesiologists; BMI, body mass index; DM, diabetes mellitus; TB, tuberculosis; HBV, hepatitis B virus; HCD, herniated cervical disc.

Table 2. Operation type, surgeon, tumor size, pathologic result, and TNM stage

	Moderate NMB (n = 44)	Deep NMB (n = 43)	P-value
Operation type			0.730
HT	2 (4.5)	4 (9.3)	
HT with CCND	36 (81.8)	33 (76.7)	
BTT with CCND	6 (13.6)	6 (14.0)	
Surgeon			0.800
Dr. Nam	26 (59.1)	28 (65.1)	
Dr. Kang	16 (36.4)	14 (32.6)	
Dr. Lee	2 (4.6)	1 (2.3)	
Tumor size (cm)	0.9 ± 0.8	1.4 ± 1.5	0.052
Pathology			0.069
Benign	4 (9.1)	5 (11.6)	
PTC, conventional	40 (90.9)	32 (74.4)	
PTC, follicular variant	0 (0)	4 (9.3)	
PTC, hobnail variant	0 (0)	1 (2.3)	
FTC	0 (0)	1 (2.3)	
TNM stage [1]			
T stage			0.037*
T1	39 (97.5)	33 (86.8)	
T2	0 (0)	4 (10.5)	
T3a	0 (0)	1 (2.6)	
T3b	1 (2.5)	0 (0)	
N stage			0.901
N0	28 (70.0)	25 (65.8)	
N1a	11 (27.5)	12 (31.6)	
N1b	1 (2.5)	1 (2.6)	
M stage			> 0.999
M0	40 (100)	38 (100)	

[1] Data for the TNM stage consisted of 78 patients (Moderate NMB = 40, Deep NMB = 38). Values are mean ± standard deviation, or number of patients (%). * $p < 0.05$ compared to the moderate NMB group. Abbreviations: NMB, neuromuscular block; HT, hemithyroidectomy; BTT, bilateral total thyroidectomy; CCND, central compartment neck dissection; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; TNM, tumor-node-metastasis.

Table 3. Perioperative data

	Moderate NMB (n = 44)	Deep NMB (n = 43)	P-value
Operation time (min)	99 ± 16	102 ± 24	0.577
Anesthesia time (min)	130 ± 17	132 ± 23	0.651
Fluid input (ml)	550 ± 117	564 ± 175	0.664
Propofol (mg)	101 ± 16	104 ± 15	0.398
Rocuronium (mg)	57 ± 9	110 ± 28	< 0.001*
Remifentanil (μg)	414 ± 132	416 ± 127	0.959
Sugammadex (mg)	121 ± 17	244 ± 39	< 0.001*
Blood Pressure (mmHg)			
Baseline	89 ± 13	90 ± 12	0.731
Before incision	72 ± 11	75 ± 10	0.331
Docking robot	75 ± 9	78 ± 9	0.201
Undocking robot	69 ± 9	70 ± 7	0.364
Heart Rate (beats/min)			
Baseline	78 ± 13	74 ± 13	0.167
Before incision	86 ± 12	85 ± 12	0.661
Docking robot	79 ± 12	81 ± 10	0.342
Undocking robot	72 ± 11	77 ± 9	0.021*
Peak airway pressure (cmH2O)			
Before incision	13 ± 2	14 ± 2	0.211
Docking robot	14 ± 1	15 ± 2	0.416
Undocking robot	13 ± 1	13 ± 2	0.655
TOF 0.9 time (sec)	99 ± 43	147 ± 78	0.001*
PACU time (min)	39 ± 15	39 ± 12	0.852
ICU admission	0 (0)	0 (0)	> 0.999
Respiratory failure	0 (0)	0 (0)	> 0.999
Desaturation	0 (0)	0 (0)	> 0.999
Postoperative bleeding	0 (0)	1 (2.3)	0.494
PONV (0-3)			
PACU	0.6 ± 0.9	0.4 ± 0.8	0.398
POD 1	0.0 ± 0.3	0.1 ± 0.4	0.510
POD 3	0.0 ± 0.2	0.0 ± 0.0	0.323

Values are mean ± standard deviation, or number of patients (%). * $p < 0.05$ compared to the moderate NMB group. Abbreviations: NMB, neuromuscular block; TOF, train-of-four; PACU, post-anesthesia care unit; ICU, intensive care unit; PONV, postoperative nausea and vomiting; POD, postoperative day.

The linear mixed models for NRS pain scores in the chest, neck, and axilla all showed significant intergroup differences over time ($p = 0.003$ in the chest; $p = 0.001$ in the neck; $p = 0.002$ in the axilla). In the post hoc analysis, the NRS pain scores of the chest, neck, and axilla were significantly lower in the deep NMB group on POD 1 compared to the moderate NMB group. (3.6 vs. 1.6 in chest, adjusted $p < 0.001$; 3.3 vs. 1.4 in neck, adjusted $p < 0.001$; 4.0 vs. 2.4 in axilla, adjusted $p < 0.001$) (Fig. 3).

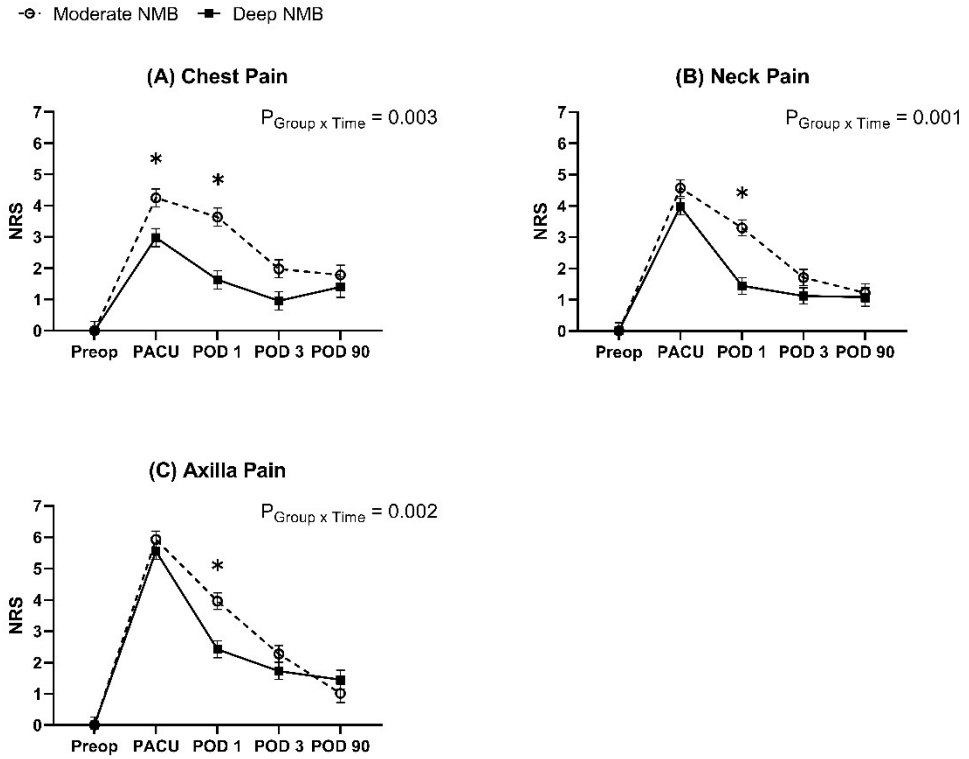

Figure 3. Changes in pain scores. The graph represented the changes in the estimated mean pain scores by linear mixed models, and error bars represented standard errors. Pain scores were expressed as numeric rating scale of 0−10 (0 = no pain and 10 = severe pain). *Bonferroni corrected $p < 0.05$ compared to the moderate NMB group. Abbreviations: NRS, numeric rating scale; NMB, neuromuscular block; Preop, preoperative; PACU, post-anesthesia care unit; POD, postoperative day.

The linear mixed models for paresthesia scores and degree of remnant sensation did not show intergroup differences over time. The paresthesia score of the chest on POD 1 was significantly lower in the deep NMB group in the post hoc analysis compared to the moderate NMB group. (3.1 vs. 2.3, adjusted p = 0.049) (Fig. 4).

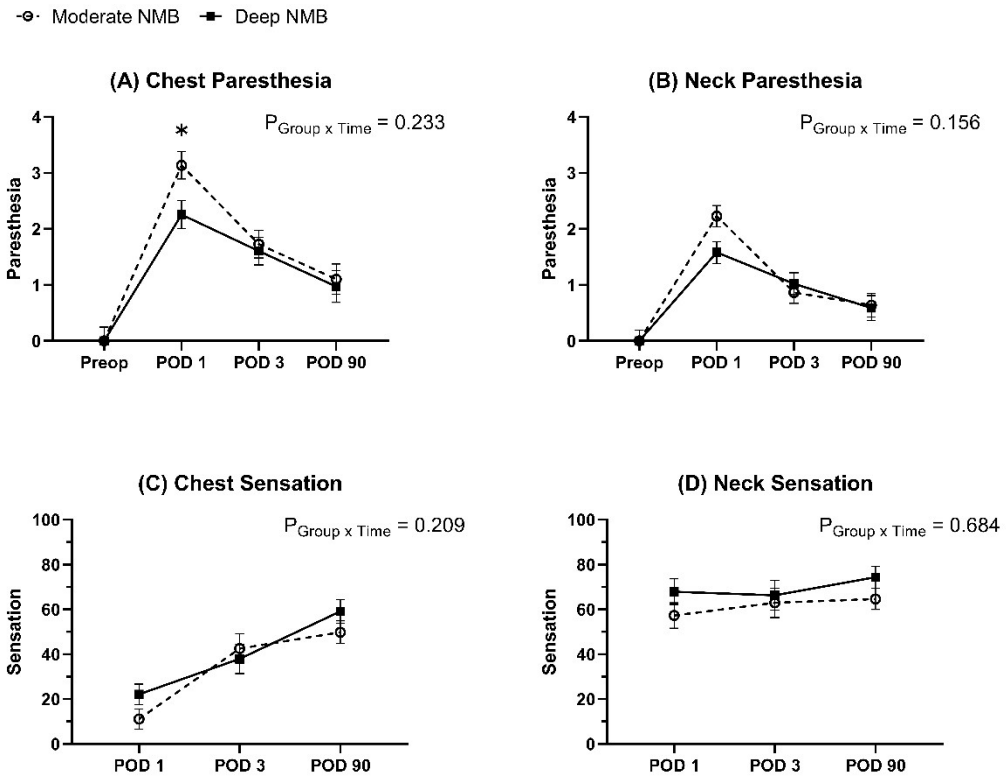

Figure 4. Changes in paresthesia scores and remnant sensation. The graph represented the changes in the estimated mean of paresthesia scores and the estimated mean of remnant sensation by linear mixed models. Error bars represented standard errors. Paresthesia scores were expressed as a scale of 0–7 (0 = no paresthesia and 7 = severe paresthesia), and the degree of remnant sensation was expressed as a percentage of 0−100%. (0 = no sensation, 100% = complete sensation). * Bonferroni corrected $p < 0.05$ compared to the moderate NMB group. Abbreviations: NMB, neuromuscular block; Preop, preoperative; PACU, post-anesthesia care unit; POD, postoperative day.

IV. DISCUSSION

This was the first investigation on the effects of deep NMB in RATT. This study demonstrated that deep NMB could reduce postoperative pain after RATT; however, it could not demonstrate that deep NMB reduces paresthesia or hypoesthesia after surgery.

The mechanisms underlying pain and sensory changes after RATT remain unknown. However, some researchers have argued that the retractor system may be involved.[5,10] RATT includes skin flap formation over the pectoralis major muscle, followed by flap elevation using an external retractor system to make a working space without carbon dioxide insufflation.[6,8,9] (Fig. 1) However, vigorous flap elevation exerts significant pressure on the skin flap, and this may cause tissue damages or nerve injuries in the anterior chest.[5,10] It is well known that nerve injury causes neuropathic pain or paresthesia through nociceptor sensitization,[19-21] and tissue damage also causes neuropathic pain or hyperalgesia by releasing various inflammatory mediators.[19,22,23] We speculated that lowering the retractor pressure in RATT could reduce tissue damage or nerve injury, mitigating postoperative pain and sensory change.

One of the factors responsible for the high retractor pressure is insufficient muscle relaxation, and previous studies have reported that deep NMB significantly lowers the retractor pressure during spinal surgery.[24] Deep NMB presumably lowers the retractor pressure in RATT by enabling sufficient relaxation of the muscles in the neck and chest. As expected, deep NMB effectively reduced postoperative pain after RATT in the current study. Considering that postoperative pain delays recovery and discharge,[25] maintaining deep NMB during RATT may improve postoperative recovery, which should be demonstrated in further studies.

We could not demonstrate that deep NMB reduces paresthesia or hypoesthesia after RATT. Considering that the deep NMB group showed a trend of less paresthesia and sensory change, significant results may be obtained if a larger number of participants were investigated, or a longer follow-up was conducted.

This study also demonstrated that deep NMB could be safely maintained during RATT without severe complications or intensive care unit admission. Nevertheless, two cases of postoperative bleeding occurred in the deep NMB group, including the dropped patient. Although we did not observe significant intergroup differences in the incidence of postoperative bleeding, it is noteworthy that the bleeding events occurred only in the deep NMB group. Some studies have reported that sugammadex increases bleeding tendency by prolonging the activated partial thromboplastin time and prothrombin time.[26-28] Given that sugammadex was administered at larger doses in the deep NMB group, it is possible that sugammadex played a role in the occurrence of postoperative bleeding.

This study has several limitations. First, most outcomes in this study were subjective indicators. Pain was measured using the NRS, and paresthesia was assessed using a questionnaire. The pinprick test relied on the subjective expression of the degree of remnant sensation by patients. Future studies should aim to confirm the effects of deep NMB through more objective indicators. Second, POD 90 data had missing values in 18 patients; hence, more participants are necessary to investigate the effects of deep NMB on chronic pain and sensory changes three months after the surgery. Larger and longer scale studies would provide a more accurate evaluation of the effects of deep NMB on chronic symptoms after RATT.

V. CONCLUSION

Deep NMB effectively reduced postoperative pain after RATT. However, this study could not demonstrate that deep NMB reduces paresthesia or sensory changes after the surgery.

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ABSTRACT(IN KOREAN)

로봇을 이용한 내시경 갑상선 절제술을 받는 환자에서 수술 중 깊은 근이완이 수술 후 통증 및 감각 변화에 미치는 효과; 전향적 무작위 배정 연구

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배경

액와 접근 로봇 갑상선 절제술 (Robot-assisted transaxillary thyroidectomy) 후 상당한 통증 및 이상 감각, 감각 저하가 발생한다는 것이 여러 연구에서 보고되어 왔다. 그리고 일부 환자들은 수술 후 3개월이 지나서도 만성적인 증상을 경험하는 것으로 보고되었다. 본 저자는 이 수술에서 깊은 근이완 (Deep neuromuscular block) 을 적용하면, 흉부 피판 (flap) 상승에 필요한 견인기 압력이 감소하며, 수술 후 통증 및 감각 변화가 감소할 것이라고 예상하였다. 본 연구는 액와 접근 로봇 갑상선 절제술에서, 깊은 근이완이 수술 후 통증 및 감각 변화에 미치는 영향에 대해 알아보고자 한다.

방법

이 연구는 단일 맹검, 전향적, 무작위 대조 연구로 설계되었다. 액와 접근 로봇 갑상선 절제술을 받는 88명의 환자들을 대상으로 하였고, 환자들은 중등

도 근이완 그룹 또는 깊은 근이완 그룹으로 무작위 할당되었다. 수술 종료 후 대상자들의 통증, 이상 감각, 잔여 감각 등을 평가하였다.

결과

숫자 평가 척도 (Numeric rating scale) 로 평가된 통증 점수에 대한 선형 혼합 모형 (Linear mixed model) 분석 결과, 흉부, 경부, 액와 모든 부위에서 두 그룹 사이에 시간에 따른 변화가 유의미하게 차이 있었다. 사후 분석 결과, 깊은 근이완 그룹의 수술 후 1일째 흉부, 경부, 액와 부위의 통증 점수가 중등도 근이완 그룹에 비해 유의미하게 더 낮았다.

결론

액와 접근 로봇 갑상선 절제술에서 깊은 근이완을 적용할 경우, 수술 후 통증이 유의미하게 감소하였다. 반면, 수술 후 이상 감각이나 감각 저하의 감소는 확인할 수 없었다.

핵심되는 말 : 로봇을 이용한 내시경 갑상선 절제술, 액와 접근 로봇 갑상선 절제술, 깊은 근이완, 수술 후 통증