ORIGINAL ARTICLE

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Comparison between the effects of deep and moderate neuromuscular blockade during transurethral resection of bladder tumor on endoscopic surgical condition and recovery profile: a prospective, randomized, and controlled trial

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Abstract

Purpose   To compare between deep neuromuscular blockade (NMB) and moderate NMB with respect to endoscopic surgical conditions and recovery profiles in patients with general anesthesia for transurethral resection of bladder (TURB).

Methods   108 patients undergoing elective TURB were randomized into two groups: the moderate NMB ($n = 54$) or deep NMB ($n = 54$) group. After the operation, NMB was reversed with 2 mg/kg sugammadex at a train-of-four (TOF) count of 1 or 2 (moderate NMB group) or with 4 mg/kg sugammadex at post-tetanic count (PTC) of 2 (deep NMB group). Surgeons, who were blinded to the study design, rated the endoscopic surgical condition on a 5-point scale (1 = extremely poor, 2 = poor, 3 = acceptable, 4 = good, 5 = optimal) immediately following the operation. Recovery profiles, including postoperative residual curarization (PORC), respiratory complication, and recovery time, were recorded.

Results   No difference was observed between the two groups regarding patients and anesthesia characteristics. There were statistically significant differences in endoscopic surgical conditions between the two groups ($P < 0.001$). Thirty-eight patients in the deep NMB group (74%) showed optimal surgical conditions, whereas 16 patients in the moderate NMB group (30%) showed optimal endoscopic surgical conditions. No PORC and respiratory complications occurred in both groups, and no difference was found between the two groups in terms of recovery profiles, including recovery time and other adverse events.

Conclusions   Deep NMB and reversal with sugammadex improved the endoscopic surgical condition without complications compared with moderate NMB and reversal with sugammadex in patients undergoing TURB.

Keywords   Bladder cancer · Endoscopic surgery · Neuromuscular blockade · Surgical space condition

Abbreviations
ASA   American Society of Anesthesiologists physical status classification
BMI   Body mass index
PACU   Post-anesthetia care unit
PTC   Post-tetanic count
TOF   Train-of-four

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Introduction

Transurethral resection of the bladder tumor (TURB) is the mainstream treatment for bladder cancer. TURB may be performed under regional anesthesia or general anesthesia. The analysis of the advantages and disadvantages of regional anesthesia compared to general anesthesia is immensely complicated. A consultation of the urologist

with the anesthesiologist is advocated in terms of types of anesthesia considering more specific information about the patient's disease and clinical profiles. During regional anesthesia, obturator nerve block may be needed to prevent adductor contraction and possible inadvertent bladder perforation in patients with large neoplasms of the lateral walls of the bladder [1, 2]. Additionally, spinal anesthesia for elderly patients may be difficult to be performed since the normal aging process is associated with degenerative anatomical changes of the spine [3]. General anesthesia with neuromuscular blockade (NMB) is conduced when regional anesthesia cannot be performed or when patients prefer not to be conscious during the surgery.

During general anesthesia for TURB, NMB is needed for intubation and optimal endoscopic surgical condition via obturator nerve block. TURB is a relatively short procedure, but patients with NMB usually require sufficient time to be reversed with conventional NMB reversal agents (anticholinesterases). Additionally, inadequate reversal from NMB may lead to respiratory complications during recovery [4]. Sugammadex, a newer reversal agent, is a selective relaxant-binding agent that allows for rapid reversal of rocuronium-induced NMB [5]. With the introduction of sugammadex, immediate reversal of deep NMB has become possible without residual NMB [6].

Several previous studies evaluated the effect of NMB on surgical condition for relative short surgeries, such as laparoscopic cholecystectomy or laryngeal micro-surgery [7–9]. They suggested that deep NMB and reversal with sugammadex improved surgical condition without postoperative respiratory complications [7, 9]. TURB is a urological endoscopic procedure performed in a narrow bladder space; however, the beneficial effects of deep NMB with sugammadex reversal for TURB have not been thoroughly evaluated. We hypothesized that deep NMB and the use of sugammadex as a reversal agent may be associated with better endoscopic surgical condition compared with moderate NMB during TURB. Therefore, this study was designed to make a comparison between deep NMB and moderate NMB with respect to the surgical conditions and recovery profiles in patients undergoing TURB via general anesthesia.

Materials and methods

Study

This study was a single center, randomized, controlled, and double-blinded trial. The protocol of this study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No B-1701-1378-006) and registered at http://www.clinicaltrials.gov (NCT#03039543). Informed

consent was obtained from all participating patients in this study.

Patients

Patients aged more than 19 years scheduled to undergo elective TURB with a physical status of I or II according to the ASA were included in this trial. The exclusion criteria were a history of neuromuscular, renal, or hepatic disease, a BMI of < 18.5 or > 30.0 kg/m^2, and treatment with drugs known to interfere with neuromuscular function.

Randomization and intervention

Randomization is conducted by a person who was not involved in the study, using a computer-generated randomization code (Random Allocation Software, version 2.0). The result of randomization was sealed in an opaque envelope, which was delivered to the anesthesiologist who oversaw patients. Patients, surgeons, and outcome assessors for recovery profiles were blinded to the group assignment. However, the anesthesiologist responsible for patients during surgery was not blinded to the assigned group. From a table of random numbers, a total of 108 patients undergoing elective TURB were randomized into either the moderate NMB group ($n = 54$) or the deep NMB group ($n = 54$).

Moderate NMB group: During maintenance of anesthesia, the added bolus doses of intravenous rocuronium (5–10 mg) were used to maintain moderate NMB (TOF count of 1 or 2) if needed. After the surgery, patients were reversed with 2 mg/kg sugammadex at a TOF count of 1 or 2.

Deep NMB group: During maintenance of anesthesia, the added bolus doses of intravenous rocuronium (5–10 mg) were used, as necessary, to maintain deep NMB (TOF count of 0 with PTC of 2). After the surgery, patients were reversed with 4 mg/kg sugammadex at PTC of 2.

Anesthesia

Intravenous midazolam (0.02 mg/kg) was administered as a premedication at the reception area of operating theater and then transferred to the operating room. In the operating room, standard monitoring, including electrocardiography, noninvasive arterial pressure measurements, and pulse oximetry, was placed. The level of NMB was monitored using acceleromyography (TOF-Watch® SX, Organon Ireland Ltd., a subsidiary of Merck & Co., Inc., Swords, Co. Dublin, Ireland) at the adductor pollicis muscle. The TOF ratio was recorded for each patient every 5 min during the operation. The TOF-watch was calibrated in each patient before performing the measurements. The stimulation current was set to 30 mA and the TOF-watch SX was calibrated in the

calibration 1 mode. During induction of anesthesia, patients received propofol (2 mg/kg) and alfentanil and the I-gel™ (Intersurgical Ltd, Wokingham, UK) was inserted after the administration of 0.6 mg/kg rocuronium in both groups. Anesthesia was maintained with desflurane, while monitoring the bispectral index (A-2000 BISTM monitor; Aspect Medical Systems, Inc., Natick, MA, USA) between 40 and 60. A bolus dose of intravenous rocuronium (5–10 mg) was used to maintain moderate (moderate NMB group, TOF count of 1 or 2) or deep (deep NMB group, TOF count of 0 with PTC of 2) NMB if needed. At the end of the operation, a surgeon rated the endoscopic surgical condition on a 5-point scale (1 = extremely poor, 2 = poor, 3 = acceptable, 4 = good, 5 = optimal, Table 1) [10]. Patients in the moderate NMB group were reversed with 2 mg/kg sugammadex at a TOF count of 1 or 2 (group A) and patients in the deep NMB group were reversed with 4 mg/kg sugammadex at PTC of 2 (group B). Patients were extubated when spontaneous ventilation was adequate. After the surgery, patients were transferred to the PACU.

Postoperative residual curarization (PORC, TOF ratio < 0.9) was recorded if it occurred. Patients were evaluated every 15-min interval using the modified Aldrete scoring system until ready for discharge from the PACU; the criterion used for patient discharge was achieving a modified Aldrete score of 9 [11]. Respiratory complications, such as desaturation ($SpO_2 < 90\%$) and respiratory depression (RR < 8), as well as other adverse events, including postoperative nausea and/or vomiting (PONV), were recorded during PACU stay.

Outcome measurement

The primary outcome was endoscopic surgical condition that was evaluated right after the operation by a surgeon (Table 1), who was blinded to the group assignment. Secondary outcomes were recovery profiles, including the postoperative residual curarization (PORC, TOF ratio < 0.9), respiratory complications, recovery time (PACU discharge, a modified Aldrete score of 9), and other postoperative adverse events. Surgical complications including bladder obturator reflex, hemorrhage, and perforation were recorded.

Statistical analysis

The sample size was calculated based on the preliminary data using G*Power 3.1.2 (Heinrich-Heine University, Düsseldorf, Germany). The proportion of optimal endoscopic surgical condition (score 5) during TURB was 30% after the use of moderate NMB ($n = 10$) and 30% increase of optimal endoscopic surgical condition by deep NMB was considered to be clinically significant. Fifty-four (54) patients per group was calculated with $\alpha = 0.05$ and $\beta = 0.2$, allowing for a 10% drop-out rate.

All statistical analyses were performed using SPSS 21 for Windows (SPSS Inc., Chicago, IL, USA), and the test of normal distribution was assessed via Shapiro–Wilk test. Chi-square test or Fisher's exact test was used to analyze the incidence variables (gender, ASA physical class, additional rocuronium, surgical condition score, PORC, respiratory complications, and other adverse events). Student's t test was used to compare the normally distributed continuous variables (age, weight, height, BMI, operation time, anesthesia time, propofol, alfentanil, rocuronium, and recovery time). All values are presented as the number of patients (%) or mean (SD). A P value of less than 0.05 was considered to indicate statistical significance.

Results

Of the 129 eligible patients, 21 patients were excluded (6: patients' refusal; 12: exclusion criteria; 3: co-operation); hence, a total of 108 patients participated in the current

Table 1 Endoscopic surgical condition score [10]

Score	Surgical condition	
1.	Extremely poor conditions	The surgeon is unable to work because of coughing or because of the inability to obtain an endoscopic view because of inadequate muscle relaxation. Additional neuromuscular blocking agents must be given
2.	Poor conditions	There is an endoscopic view but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions, movements, or both with the hazard of tissue damage. Additional neuromuscular blocking agents must be given
3.	Acceptable conditions	There is a wide endoscopic view but bladder contractions, movements, or both occur regularly causing some interference with the surgeon's work. There is the need for additional neuromuscular blocking agents to prevent deterioration
4.	Good conditions	There is a wide endoscopic working field with sporadic muscle contractions, movements, or both. There is no immediate need for additional neuromuscular blocking agents unless there is the fear of deterioration
5.	Optimal conditions	There is a wide endoscopic working field without any movement or contractions. There is no need for additional neuromuscular blocking agents

study. Among them, 54 patients were assigned to the moderate NMB group and 54 to the deep NMB group. One patient in the moderate NMB group and 3 patients in the deep NMB group were excluded from the final analysis (1 in deep NMB group: unexpected co-operation; 1 in moderate NMB group and 2 in deep NMB group: did not maintain moderate or deep NMB); thus, the data of 104 patients were used for the final analysis (Fig. 1). Between the two groups, there was no statistically significant difference with respect to patients, surgery and anesthesia characteristics, except the total dose of rocuronium (Table 2).

There were statistically significant differences in the surgical condition between the two groups ($P < 0.001$). Optimal surgical condition was observed in 38 (74%) patients of the deep NMB group and in 16 (30%) patients in the moderate NMB group (Table 3). Obturator reflex occurred more frequently in the moderate NMB group than in the deep NMB group (11 vs. 1; $P = 0.007$, Table 3). During postoperative 7 days, hemorrhage occurred in 4 patients (1 in the moderate NMB group and 3 in the deep NMB group). During TURB, mild lateral wall perforation was observed in 1 patient of the deep NMB group (Table 3).

After anesthesia, no difference was observed between the two groups in terms of recovery profiles, including the PORC, respiratory complication, recovery time (PACU discharge time), and other postoperative adverse events. No drug adverse events occurred during the study period (Table 3).

Discussion

We set out this first randomized and controlled trial to determine whether deep NMB affects endoscopic surgical space condition during TURB. The results of the current study suggest that deep NMB, when compared with moderate NMB, during TURB and reversal of NMB with sugammadex after surgery improved the urologic endoscopic surgical condition without postoperative respiratory complication.

This study was performed for patients undergoing TURB with general anesthesia. In our institution, general anesthesia is mainly performed for elderly patient with TURB for the following reasons although general anesthesia cannot be considered as a gold standard anesthetic methods for elderly patients with TURB. First, general anesthesia with propofol and desflurane facilitates shorter induction and recovery times without adversely affecting patient comfort [12]. Second, spinal anesthesia for elderly patients may be difficult to

Fig. 1 Consort flow diagram of the patients. Of the 129 eligible patients, 21 patients were excluded and a total of 108 patients participated in the current study, of which, 54 were assigned to the moderate neuromuscular blockade (NMB) group and 54 to the deep NMB group. One patient in the moderate NMB group and 3 patients in the deep NMB group were excluded from the final analysis (1 in deep NMB group: unexpected co-operation; 1 in moderate NMB group and 2 in deep NMB group: did not maintain moderate or deep NMB) and the data of 104 patients were used for the final analysis
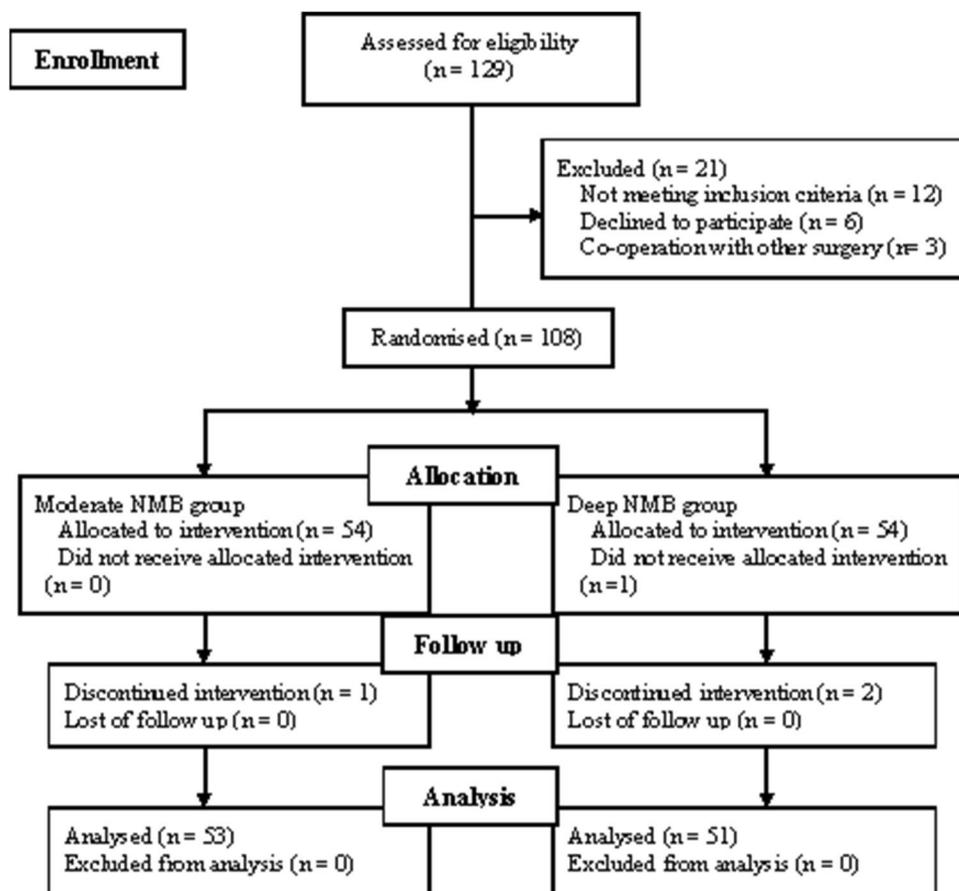
Table 2 Patients and anesthesia characteristics

	Moderate NMB ($n=53$)	Deep NMB ($n=51$)	P value
Age, years	70 (11)	68 (10)	0.568
Male/female, %	46 (87)/7 (13)	42 (82)/9 (18)	0.594
Weight, kg	66 (10)	67 (11)	0.729
Height, cm	165 (7)	165 (8)	0.977
BMI, kg/m^2	24 (3)	25 (4)	0.670
ASA class, I/II	18 (34)/35 (66)	17 (33)/34 (67)	> 0.999
Operation time, min	23 (13)	22 (13)	0.924
Tumor number, n	2 (5)	2 (4)	0.399
Tumor size, mm	20 (15)	20 (20)	0.898
Tumor location			0.050
Lateral	13 (25)	19 (37)	
Trigone	18 (34)	22 (43)	
Multiple	22 (42)	10 (20)	
Tumor stage			0.233
No cancer	13 (25)	12 (24)	
pTa	20 (38)	22 (43)	
pT1	12 (23)	11 (22)	
pT2	8 (15)	6 (12)	
Tumor grade			> 0.999
No cancer	13 (25)	12 (24)	
Low	12 (23)	19 (37)	
High	28 (47)	20 (39)	
Anesthesia time, min	46 (16)	45 (15)	0.879
Rocuronium (total, mg)	42 (7)	46 (10)	0.035
Additional rocuronium (n)			0.534
0	38 (72)	32 (63)	
1	11 (21)	13 (25)	
2	3 (6)	5 (10)	
3	1 (2)	0 (0)	
4	0 (0)	1 (2)	

Values are given as mean (SD) or number of patients (%) except tumor number and size (median [range])

BMI body mass index, *ASA class* American society of Anesthesiologist physical class

be performed since the normal aging process is associated with degenerative anatomical changes of the spine (e.g., vertebral collapse, osteophytes, calcified ligamentum flavum) [3]. Additionally, the abrupt hemodynamic changes associated with sympathetic blockade following spinal anesthesia may adversely affect the compromised elderly patient [3].

The current study was specifically aimed at scoring urological endoscopic procedures performed in a narrow bladder space. We found that 74% of patients with deep NMB, versus 30% of patients with moderate NMB, showed optimal endoscopic surgical conditions during TURB. The result of the present study is in line with previous investigations evaluating the effect of NMB on surgical conditions during short procedures, such as laparoscopic cholecystectomy and laryngeal micro-surgery [7, 9]. They showed that the maintenance of deep or adequate NMB during the operation and NMB reversal with sugammadex

after the surgery were associated with better surgical conditions compared with moderate NMB and neostigmine reversal [7, 9].

TURB is a relatively short procedure, commonly performed in geriatric patients. During general anesthesia for TURB, NMB is needed for intubation and optimal surgical condition via obturator nerve block. Rocuronium is the most commonly used muscle relaxant, and it has a rapid onset and a prolonged duration of action at higher doses. Patients with NB usually require sufficient time for reversal with conventional NMB reversal agents (anticholinesterases). Inadequate reversal from NMB and early extubation may lead to inadequate respiratory muscle power and subsequent respiratory complications during recovery due to PORC [4]. Sugammadex is a selective relaxant-binding agent that allows for rapid reversal of rocuronium-induced NMB [13]. Thus, there is now no reason to avoid adequate NMB during

Table 3 Endoscopic surgical condition score, surgical complications and recovery profiles

	Moderate NMB ($n=53$)	Deep NMB ($n=51$)	P value
Endoscopic surgical condition score			<0.001
1. Extremely poor conditions	0 (0)	0 (0)	
2. Poor conditions	0 (0)	0 (0)	
3. Acceptable conditions	13 (25)	2 (4)	
4. Good conditions	24 (45)	11 (22)	
5. Optimal conditions	16 (30)	38 (74)	
Obturator reflex	11 (21)	1 (2)	0.007
Perforation	1 (2)	3 (6)	0.583
Hemorrhage	0 (0)	1 (2)	0.985
PORC	0 (0)	0 (0)	>0.999
Recovery time, min	15 (0)	15 (0)	>0.999
Respiratory complication	0 (0)	0 (0)	>0.999
Other adverse events	0 (0)	0 (0)	>0.999

Values are given as number of patients (%)

PORC postoperative residual curarization, *recovery time* time needed for the achievement of modified Aldrete score of 9 that was assessed every 15 min

general anesthesia for TURB if sugammadex is available as a reversal agent.

In the current study, no PORC (TOF ratio <0.9) and respiratory complications, such as respiratory depression or desaturation, occurred in the PACU for both groups, which may be explained by the use of sugammadex in both groups as a reversal agent. The incidence of PORC was reported to be 50%, even after the use of intermediate-acting muscle relaxants and reversal with anticholinesterase [14]. PORC during PACU stay is associated with a greater incidence of major and minor respiratory complications and the use of sugammadex as an NMB reversal agent significantly reduces the incidence of PORC in the PACU [15]. Moreover, TURB is frequently performed in elderly patients; the mean age of the patients was 69 (SD 11) years across both groups. Therefore, in this study, adequate NMB during TURB and reversal using sugammadex likely resulted in better endoscopic surgical conditions without the possibility of postoperative respiratory complications.

The current study has a few limitations to be considered. First, this study was performed for patients undergoing TURB with general anesthesia though general anesthesia for TURB cannot be considered as a gold standard for elderly patients. In our institution, general anesthesia is chosen after cooperation of the urologist with the anesthesiologist due to rapid recovery of anesthesia. Second, an evaluation of the endoscopic surgical condition was performed by a urologic surgeon right after the surgery to maintain blindness. Ideally,

it is needed for a few surgeons to review the video after surgery and to agree on the scores of the overall condition of the surgical space to reduce inter-rater reliability and variability in surgical rating.

Conclusion

This is the first prospective, randomized, controlled study to investigate the effect of NMB on the urologic endoscopic surgical conditions in patients undergoing TURB. Deep NMB with sugammadex reversal improved urologic endoscopic surgical conditions without postoperative complications compared with moderate NMB in patients undergoing TURB. It is suggested that sugammadex could be a useful reversal agent in elderly patients undergoing TURB after adequate NMB during general anesthesia.

Compliance with ethical standards

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