



Current use of neuromuscular blocking agents and antagonists in Korea: a 2018 survey

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Background: Neuromuscular blocking agents (NMBAs) and neuromuscular monitoring in anesthetic management are integral for endotracheal intubation, better visualization of the surgical field, and prevention of residual neuromuscular blockade and pulmonary complications. Sugammadex is a drug that reduces risk of residual neuromuscular blockade, with more rapid recovery compared to anticholinesterase. The purpose of this study was to investigate current usage status of NMBAs and antagonist with neuromuscular monitoring, among anesthesiologists in Korea.

Methods: Anesthesiologists working in Korea were invited to participate in an online survey via email January 2–February 28, 2018. The questionnaire consisted of 45 items, including preferred NMBAs, antagonists, neuromuscular monitoring, and complications related to the use sugammadex. A total of 174 responses were analyzed.

Results: Rocuronium was a commonly used NMBA for endotracheal intubation (98%) of hospitals, and maintenance of anesthesia (83.3%) in of hospitals. Sugammadex, pyridostigmine, and neostigmine were used in 89.1%, 87.9%, and 45.4% of hospitals. Neuromuscular monitoring was employed in 79.3% of hospitals; however only 39.7% of hospitals used neuromuscular monitoring before antagonist administration. Usual dosage range of sugammadex was 2.1–4 mg/kg in 35.1% of hospitals, within 2 mg/kg in 34.5% of hospitals, and 1 vial regardless of body weight in 22.4% of hospitals. Sugammadex-related complications were encountered by 14.9% of respondents.

Conclusions: This survey indicates several minor problems associated with the use of antagonists and neuromuscular monitoring. However, most anesthesiologists appear to have appropriate information regarding the usage of NMBAs and sugammadex.

Keywords: Neostigmine; Neuromuscular blocking agents; Neuromuscular monitoring; Pyridostigmine bromide; Sugammadex.

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INTRODUCTION

During anesthetic management, neuromuscular blocking agents (NMBAs) can enhance ease of endotracheal intubation, field of view, and operating conditions while reducing the dose of inhalation or intravenous anesthetic agents and are also essential for respiratory management for intraoperative controlled mechanical ventilation [1,2]. Furthermore, neuromuscular monitoring and antagonist administration are important for preventing complications of residual neuromuscular blockade, such as dyspnea, hypoxia, atelectasis, and pneumonia [3]. Particularly, neuromuscular monitoring provides important information for neuromuscular dose adjustment, neuromuscular action for endotracheal intubation, timing of antagonist administration postoperatively, and determination of its dose. The use of antagonists during recovery for patients who received NMBAs restores spontaneous breathing and prevents residual neuromuscular blockade and recurarization by adequately recovering muscle strength (train-of-four ratio [TOFr] > 0.9) [4,5].

Sugammadex is an antagonist of the aminosteroid non-depolarizing neuromuscular blockers vecuronium and rocuronium; compared to anticholinesterases, it is an effective drug that promotes and quick recovery while lowering the risk of residual neuromuscular blockade [6]. In Korea, it has been introduced in 2013. Thus, it was considered possible that there might have been changes in the use of NMBAs and antagonists in clinical practice.

We hereby report a survey of the selection of NMBAs for endotracheal intubation and anesthesia maintenance, the usage of neuromuscular monitoring and choice of antagonists well as anesthesiologists' update concepts in Korea.

MATERIALS AND METHODS

An anonymous questionnaire was administered to anesthesia specialists and residents in clinical practice who are registered members of the Korean Society of Anesthesiologists (KSA) and who live in Korea. The survey was sent via email for the anesthesiologists to complete the online survey themselves; 174 responses that were delivered via the web link (<https://goo.gl/forms/cNLvOyoftVjWfKS2>) within two months from January 2 to February 28, 2018 were analyzed.

Participants were instructed to give either a single response

or three responses in order of preference, depending on the type of question; the assessment was made based on the popular responses. In some instances, the total number of responses could exceed 174, due to duplicate responses, so the sum of responses was computed with the sum of duplicate responses and presented as percentage of total number. The survey consisted of 45 items, including demographic information such as length of career at the hospital, features of the hospital, and area of residence, as well as information about application of NMBAs and neuromuscular monitoring devices, preference for NMBA antagonists, current use of sugammadex, and its complications.

RESULTS

Table 1 shows the details of anesthesiologists who participated in the survey.

Rocuronium was the most popular agent for endotracheal intubation and intraoperative maintenance of neuromuscular blockade (Table 2). Regarding neuromuscular reversal agents available at each hospital, sugammadex was the most common (89.1%), followed by pyridostigmine (87.9%). When asked to choose three neuromuscular block reversal agents in the order of frequent use, 142 out of 174 (80.2%; 177 cases including duplicate responses) chose anticholinesterases (pyridostigmine, n = 96 [54.2%], neostigmine n = 46 [26.0%]) as the most preferred agent, while 35 (19.8%) chose sugammadex as their primary choice. On the other hand, 101 out of 160 (63.1%) chose sugammadex as the second-most preferred antagonist, while 39 (24.4%) chose pyridostigmine and 20 (12.5%) chose neostigmine. The most popular combination of anticholinergics used with anticholinesterases was pyridostigmine + glycopyrrolate, followed by neostigmine + glycopyrrolate and neostigmine + atropine. The reasons for not using antagonists were "because NMBAs are not used at all" (30.5%), "because patient seemed adequately recovered or an adequate amount of time has passed" (26.4%), and "complete recovery was confirmed using monitoring devices such as TOF" (13.8%); 22.4% of participants stated that they always used neuromuscular block reversal agents.

Approximately 93.1% of the participants stated that they were aware of the cost of sugammadex. Regarding the use of sugammadex, it was used for all patients of general anesthesia by 9.8% of the respondents, only used for recommended

Table 1. Demographic Data

Question	Result
Position	
Resident trainees	38 (21.8)
Board-certified anesthesiologists	136 (78.2)
Affiliation	
University hospital	135 (77.6)
Nonteaching hospital	39 (22.4)
Years of working in anesthesiology department	
< 5	46 (26.4)
5–10	45 (25.9)
11–20	49 (28.2)
> 20	34 (19.5)
Size of hospital	
< 50 beds	7 (4.0)
50–100 beds	10 (5.8)
> 100 beds	157 (90.2)
Number of daily average general anesthesia which is performed by respondent	
< 5	83 (47.7)
5–10	69 (39.7)
10–20	18 (10.3)
> 20	4 (2.3)
Number of daily average general anesthesia which is performed in respondent's hospital	
< 5	25 (14.4)
5–10	13 (7.5)
10–20	8 (4.6)
21–50	67 (38.5)
51–100	34 (19.5)
100–200	11 (6.3)
> 200	16 (9.2)
The practice location of respondents	
Seoul	70 (40.2)
Gyeonggi-do	32 (18.4)
Busan	14 (8.0)
Incheon	10 (5.7)
Daejeon, Gangwon-do	8 (4.6) each
Daegu, Gwangju	7 (4.0) each
Ulsan	1 (0.6)
Chungcheong-do, Jeolla-do	6 (3.4) each
Gyung-sang-do	5 (2.9)
Jeju-do	0 (0)

Values are presented as number (%).

indications by 40.2%, occasionally or rarely used by 36.2%, and never used by 9.2%. The reasons for the restrictions in clinical usage included regulations such as diagnosis-related group (50.0%), price (31.1%), and limited indications (10.9%). Regarding the degree of restriction of sugammadex usage, 89.1% of the participants stated that they “use it without restrictions” or “use only for a small minority of patients,” suggesting that the majority of them are using it in clinical practice. Regarding the dosage of sugammadex, 22.4% said that

Table 2. Availability and Usage Status of Neuromuscular Blocking and Reversal Agents

Question	Result
Choose NMBA that are mainly used for endotracheal intubation (multiple selection is possible)	
Succinylcholine	17 (9.8)
Rocuronium	167 (96.0)
Vecuronium	14 (8.0)
Atracurium	2 (1.1)
Cisatracurium	44 (25.3)
Choose NMBA that is mainly used for maintenance of anesthesia	
Succinylcholine	0 (0)
Rocuronium	145 (83.3)
Vecuronium	15 (8.6)
Atracurium	1 (0.6)
Cisatracurium	13 (7.5)
Choose reversal agents of neuromuscular blockade that were prepared in your hospital (multiple selection is possible)	
Neostigmine	79 (45.4)
Pyridostigmine	153 (87.9)
Edrophonium	0 (0)
Sugammadex	155 (89.1)
If you do not use the reversal agents during recovery from anesthesia, why is that?	
Because of not use of any NMBA at all	53 (30.5)
Because sufficient time has passed since the administration of the NMBA	23 (13.2)
Because the symptoms of the patient are fully recovered	23 (13.2)
Since complete recovery was confirmed using neuromuscular monitoring device such as TOF	24 (13.8)
I always use the reversal agent	39 (22.4)
Others	12 (6.9)

Values are presented as number (%). NMBA: neuromuscular blocking agent, TOF: train-of-four.

they administer one vial (200 mg), regardless of the patient's weight or condition (Table 3).

A total of 79.3% of the participants said that their hospital was equipped with devices for monitoring neuromuscular function. Approximately 39.7% said that the monitoring device was used prior to administering antagonists, while 60.3% said that it was not. When determining the timing of antagonist administration, most participants used TOF stimulation results, while 1.2% said that they administer antagonists once surgery is concluded, regardless of the results of neuromuscular monitoring (Table 4).

Approximately 14.9% encountered adverse reactions after sugammadex administration. Types of adverse reactions included decreased systolic blood pressure below 80 mmHg,

Table 3. Availability and Usage Status of Sugammadex

Question	Result
Do you know the amount of money you need to use sugammadex?	
Yes	162 (93.1)
No	12 (6.9)
How often do you use sugammadex as an antagonist of neuromuscular blockade?	
In all patients	17 (9.8)
Use only in recommended indications	70 (40.2)
I use it occasionally	53 (30.5)
It is rarely used	10 (5.7)
I do not use it at all	16 (9.2)
Others	8 (4.6)
Do you have limited use of sugammadex, select a reason	
Due to (expensive) price	54 (31.1)
Due to regulations such as DRG, car insurance	87 (50.0)
Due to restricted indication	19 (10.9)
Due to sugammadex-related side effects	2 (1.1)
Others	12 (6.9)
If you have restrictions on using sugammadex, select a level of restriction	
None restriction	29 (16.7)
There are some limitations, but they are freely usable	82 (47.1)
Partially restricted	29 (16.7)
Used only in very few patients who have indications	15 (8.6)
Completely restricted	12 (6.9)
Others	7 (4.0)
If sugammadex is administered to antagonize the neuromuscular blockade, select a routine dosage	
≤ 2 mg/kg	60 (34.5)
2.1–3.9 mg/kg	42 (24.1)
4 mg/kg	19 (10.9)
8 mg/kg	1 (0.6)
16 mg/kg	0 (0)
One vial regardless the body weight	39 (22.4)
Others	13 (7.5)
Have you experienced any complications due to sugammadex?	
Yes	26 (14.9)
No	148 (85.1)

Values are presented as number (%). DRG: diagnosis-related group.

anaphylaxis, and increased intra-tracheal pressure (e.g., due to bronchospasm) requiring endotracheal intubation and mechanical ventilation, and reduced oxygen saturation: other adverse reactions included bradycardia, cardiac arrest, reduced vigor, perspiration, postoperative delirium, and headache. If hypoxia or dyspnea occurred after sugammadex administration, the most common causes were thought to be insufficient dose of antagonist, residual effect of narcotic analgesics, residual effects of anesthetics, residual effects of

Table 4. Application Status of Neuromuscular Function Monitoring Device

Question	Result
Does your hospital have monitoring device of neuromuscular function?	
Yes	138 (79.3)
No	36 (20.7)
Do you measure neuromuscular function recovery before administration of reversal agents?	
Yes	69 (39.7)
No	105 (60.3)
How often do you monitor neuromuscular function in your patients receiving NMBAs?	
In all patients	15 (8.6)
In 75% of patients	19 (10.9)
In 50% of patients	10 (5.7)
In 25% of patients	56 (32.2)
Only in patients with abnormal neuromuscular function (e.g., myasthenia gravis)	27 (15.5)
Only for a limited number of studies	9 (5.2)
Never	33 (19.0)
Others	5 (2.9)
If the neuromuscular monitoring is performed during surgery, select when to administer the reversal agents to reversal of the neuromuscular blockade	
Posttetanic count ≤ 5	0 (0)
Posttetanic count 6–10	0 (0)
TOF count 1	7 (4.0)
TOF count 2	36 (20.7)
TOF count 3	30 (17.2)
TOF count 4	39 (22.4)
TOF ratio ≤ 0.5	7 (4.0)
TOF ratio ≥ 0.5	19 (10.9)
TOF ratio ≥ 0.9	9 (5.2)
Others	27 (15.5)

Values are presented as number (%). NMBA: neuromuscular blocking agent, TOF: train-of-four.

NMBA and recurarization. Countermeasures included oxygen administration, additional administration of sugammadex, endotracheal intubation, placement of ventilator, administration of opioid antagonist and application of continuous positive pressure ventilation, administration of vasopressors, and treatment equivalent to cardiopulmonary resuscitation.

DISCUSSION

Anesthetic management has undergone substantial changes with the introduction of novel pharmacologic agents such as NMBAs. The present survey aimed to investigate changes of anesthesiologists' perceptions and current use of NMBAs

and antagonists, and the application of neuromuscular monitoring since the introduction of sugammadex; a total of 174 participants completed the survey. A considerable percentage of anesthesia specialists who participated in the survey (over 40%) worked in large hospitals in Seoul and Gyeonggi regions, and in other large cities, which was borne out by the proportion of their responses [7]. A total of 136 out of 4,521 anesthesia specialists (3,946 excluding those on leave; 3.4%) and 38 out of 815 anesthesiology residents nationwide participated in the survey, so the present survey has an established significance.

An ideal NMBA is a non-depolarizing agent with fast onset and short duration of action that enables fast recovery with low or non-organ dependence, and no other toxicity effects, must not be accumulated in the body, have no side effects such as cardiac arrhythmia or histamine release, and be easy to reverse [8,9]. There is currently no such NMBA available, and among NMBAs that are currently used in clinical practice, rocuronium and cisatracurium would be the closest to an ideal NMBA among aminosteroids and benzylisoquinoliniums, respectively. Particularly, rocuronium has gained preference before the introduction sugammadex that enables fast and predictable recovery [10]. In the present survey, only a handful of anesthesiologists (9.8%) chose succinylcholine as the NMBA for endotracheal intubation, while 96.0% chose rocuronium. This contrasts to the results of a 2010 survey of Korean anesthesiologists, in which 73.1% chose succinylcholine for endotracheal intubation [11]. This trend seems to be attributable to the fact that anesthesiologists prefer agents with a fast onset and easy reversal of rocuronium and vecuronium, such as sugammadex.

Among anticholinesterases, edrophonium cannot be used due to its unavailability in Korea, while neostigmine and pyridostigmine are available for use. The less frequent use of neostigmine compared to pyridostigmine seems to be attributable to a past trend. Compared to pyridostigmine, neostigmine has a faster onset but shorter duration, has a five-fold higher potency, and greater muscarinic action, although there are no differences in recovery with neuromuscular blockade [12,13]. Hence, if an anticholinesterase must be used, neostigmine, which is high potency and has a fast onset of action, is preferentially recommended [13,14]. Although there has been a report suggesting that anticholinesterase administration increases upper respiratory col-

lapsibility and risk of postoperative atelectasis after reversal of neuromuscular blockade, subsequent studies concluded that using an appropriate dose of anticholinesterase under neuromuscular monitoring was helpful in preventing postoperative respiratory complications related to NMBAs [15]. If an additional administration is needed because the initial dose of anticholinesterase did not induce complete reversal, the authors recommend that they must be used with caution, and sugammadex is recommended [6,16]. With the introduction of sugammadex, the formation of rocuronium-sugammadex complex has enabled predictable and prompt reversal of neuromuscular blockade regardless of the depth of blockade, which has not been possible with other NMBA-antagonist combinations, and as a result, catch phrases such as "So Long, Sux!" and "So Long, Neostigmine!" were introduced [4]. Currently, determining the accurate dose and timing of sugammadex with neuromuscular monitoring, and, if an emergency reoperation is needed for patients who were administered sugammadex, determining the accurate dose and timing of rocuronium has become more important as opposed to selecting an anticholinesterase [17,18]. In addition, if neuromuscular blockade is required for reoperation but cannot be achieved with rocuronium and sugammadex, benzylisoquinoliniums (e.g., cisatracurium) or succinylcholine could probably be used [6,19,20]. If cisatracurium is used, rocuronium that did not bind to sugammadex and nicotinic acetylcholine receptors that did not bind neuromuscular blockers could induce priming effects, thereby causing an earlier onset of action for cisatracurium [21].

Anticholinergics used with anticholinesterases include atropine and glycopyrrolate. In clinical practice, glycopyrrolate is generally preferred to atropine despite its lower antimuscarinic effects, which was reflected in the present survey. Takkunen et al. [22] reported that the combination of neostigmine and glycopyrrolate has less effects on the central nervous system with greater protective effects against oral secretions, such as saliva, and promotes cardiac stability due to a low risk of bradycardia and junctional arrhythmias compared to the combination of neostigmine and atropine during the reversal of neuromuscular blockade by pancuronium, but there is no difference in the incidence of postoperative nausea and vomiting [13,23].

In rare cases, antagonists are not used during recovery after the use of NMBAs. In the present survey, only 22.4% of

the respondents said that they always use an antagonist, and the rates of routine use of antagonists in Europe and United States are only 18% and 34%, respectively [14]. However, it is impossible to qualitatively and quantitatively examine the residual effects of NMBAs without using antagonists, thereby increasing the risk of residual neuromuscular blockade or recurarization [24]. Therefore, a neuromuscular monitoring device should be used for all patients who are administered NMBAs, and the use of antagonists (and if used, the type and dose of the agent) should be decided with reference to the monitoring results [24,25].

The most important factors for addressing the problems after neuromuscular blockade, such as residual neuromuscular block, recurarization, and consequent pulmonary complications, are monitoring of neuromuscular functions and administration of appropriate antagonists [26]. In the present survey, 79.3% reported that a neuromuscular monitoring device was available for clinical application at their hospital, which was similar to the rates reported in a 2010 Korean survey (available in operating room [OR]: 83.3%, available in hospital: 79.5%) [11]. Methods such as TOF are used at a frequency of 22.7% in the United States and 70.2% in Europe, and the percentage of hospitals equipped with a neuromuscular monitoring device in an OR is 71.4% in the United States and 44.5% in Europe [14]. Furthermore, the percentage of participants who do not use neuromuscular monitoring at all was 9.4% in the United States and 19.3% in Europe [14]. In Korea, the clinical application of sugammadex seems to have been influenced by insurance coverage, financial burden due to costly drug price, diagnosis-related group (DRG), and indications designated by the Ministry of Food and Drug Safety. Furthermore, only 25.3% said that they apply neuromuscular monitoring for more than 50% of all surgical patients. These results indicate that there have been no changes in the clinical application of NMBAs over the last decade, calling for the KSA and Korean Neuromuscular Research Society (KNRS) to develop, promote, and provide education with relevant guidelines.

Regarding the determination of the timing of antagonist administration, none of the participants chose tetanic stimulation and post-tetanic counts (PTC); most participants reported using TOF to determine the timing of reversal administration for performing neuromuscular monitoring. More than 90% of the participants used TOF, and they reported

administering antagonists after T2 or higher was detectable. However, some anesthesiologists administered antagonists after surgery was completed, regardless of the results of neuromuscular monitoring. Regarding the dose of sugammadex, most participants reported using one vial or less, presumably due to the high cost of the agent. Although many studies recommend administering 2.0 mg/kg of sugammadex when T2 is detectable, the dosage may be adjusted based on the PTC or TOF ratio. The authors suspect that if sugammadex is administered after T2 is detected, administering 1 vial of sugammadex without neuromuscular monitoring, based only on body weight, may lead to an unnecessary excessive dose, but anesthesiologists should take precaution as insufficient dosage in obese patients may induce residual neuromuscular blockade or re-blockade [27].

Regarding adverse reactions with sugammadex administration, we only listed the type of reactions because duplicate responses could alter the actual frequency. The causes of adverse reactions included residual effects of NMBAs, recurarization, insufficient dose of sugammadex, and hypersensitivity, but some participants mentioned the residual effects of the main anesthetic and opioid. Countermeasures included oxygen administration, additional sugammadex administration, pressor agents, endotracheal intubation and ventilation, and CPR, and anesthesiologists seem to have performed appropriate therapeutic interventions according to the severity of the adverse reactions. However, residual neuromuscular blockade and recurarization may occur after sugammadex administration, and insufficient dosage, hypersensitivity, and anticoagulation can also occur. Moreover, we must think about measures to address problems regarding interactions between sugammadex and drugs that may affect its binding affinity, as well as patients' condition and other abnormalities [27]. To resolve or prevent these problems, an accurate understanding of the timing and dosage of sugammadex is needed in addition to neuromuscular monitoring [28]. Residual neuromuscular block after sugammadex administration occurs as a result of non-routine use of neuromuscular monitoring, low usage of monitoring results, lack of standard for neuromuscular monitoring, lack of accurate data about prevalence and mortality of adverse reactions, and high costs. Furthermore, although hypersensitivity cannot be predicted, most cases occur within five minutes of administration, so changes in the patient's state immediately after administra-

tion should be carefully observed. In general, bradycardia can occur proportionally to the dose, so treatment using appropriate drugs in addition to accurate neuromuscular monitoring and dosage are crucial [29].

One limitation of this study is the possibility of bias, as the sample size was 174, which is less than 5% of the total number of registered anesthesiology specialists and residents currently working in Korea (as of 2018). Despite the small sample size and the fact that some participants work at the same hospital and thus their responses may be redundant, the study population varied in terms of job position, length of career, type of hospital, and region of work, so the findings would be helpful in understanding the current use of NMBAs, neuromuscular monitoring, and antagonists. Second, in the survey about the adverse reactions of sugammadex, the questionnaire was designed such that online submission was only possible after choosing a response even if some items were redundant or were not applicable. In such cases, we only listed the type and excluded them from analysis to eliminate the possibility of delivering wrong information, but this should be addressed in subsequent surveys.

In conclusion, based on the results of this survey, neuromuscular monitoring should be coupled with the use of NMBAs and antagonists, which are important agents for anesthetic management. Nevertheless, it seems that most anesthesiologists have the correct information about the use of neuromuscular monitoring and timing and dosage of antagonists, though there are practical difficulties for clinical application. Therefore, the KSA and the KNRS should implement and continually promote and educate anesthesiologists about guidelines for the use of neuromuscular monitoring devices according to the use of NMBAs and antagonists.

SUPPLEMENTARY MATERIALS

Supplementary data containing Korean version of this article is available at <https://doi.org/10.17085/apm.2019.14.4.441>.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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