Original Article

# Train-of-four Guard-controlled Sugammadex Reversal in Patients with Multiple Sclerosis

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**Abstract**

**Objective:** Multiple sclerosis (MS) is a chronic inflammatory and demyelinating autoimmune disease of the central nervous system. It is known that the disease, which is manifested by a wide variety of symptoms, may exacerbate after anesthesia and show different responses to muscle relaxants in the normal population. It is planned to measure train-of-four (TOF) values of MS patients to be operated under general anesthesia before sugammadex application. **Materials and Methods:** With the approval of the local ethics committee of the University of Health Sciences Bagcilar Training and Research Hospital and with written consents of participants, we anesthetized ten patients (from April 2014 to March 2017) with MS and ten American Society of Anesthesiologists I-III patients without MS. Neuromuscular conduction was assessed by the acceleromyometric method using a TOF-Guard apparatus (Organon, Holland). The patients were extubated after recovery of TOF higher than 0.9. The primary efficacy variable was the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9. **Results:** The demographic characteristics of both groups, the type and duration of surgery and anesthesia applied, and the temperature of the operation room were similar. Similar characteristics of both groups were of concern for postoperative residual paralysis, and therefore we did not notice any difference between time to TOF >90/s for both groups. **Conclusion:** Sugammadex and TOF patients will increase patient safety in general anesthesia practice.

**Keywords:** *Multiple sclerosis, sugammadex, train of four*

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## Introduction

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating autoimmune disease of the central nervous system. It has been estimated to affect as many as 2.1 million people worldwide.[1] Clinically, MS presents with four main clinical forms: relapsing remitting (RRMS), secondary progressive, primary progressive, and progressive relapsing MS.[2,3] Approximately 87% of patients present with RRMS. MS symptoms vary depending on the nerve fibers affected such as motor deficits, visual disturbances, blurred vision, sensory deficits, tremor, speech disorders, and spasticity. It is known that perioperative stress, emotional instability, anesthesia, and increased body temperature might exacerbate MS attacks.[4] Diagnosis in MS cannot be based solely on clinical symptoms. Magnetic resonance imaging (MRI), computed tomography, visual-evoked potentials, somatosensorial-evoked potentials, or lumbar puncture can be performed for diagnosis. Recent evidence suggests that endothelial microparticles detected in plasma may be a valid marker for early MS.[5] Treatment of MS is directed toward the resolution of acute attacks, prevention of recurrence, and slowing of disease progression. This is best accomplished with multidisciplinary approach targeting physical, physiological, social, and familial aspects. Oral prednisolone therapy is no longer used and intravenous (IV) methylprednisolone therapy is

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still in use.[6] Adrenocorticotropic hormone should be plasmaferesis and IVIG is used in attacks. Drugs such as interferon beta (IFNβ), glatiramer acetate, natalizumab, and fingolimod are commonly used in MS, especially in those with MS.[7,8]

For patients with relapsing forms of MS, the injectable immunomodulatory agents IFNβ-1 and glatiramer acetate (GA) are the most common initial treatment options. Interferon therapies were started on the basis that their antiviral properties might reduce the environmental triggers of MS.[9] A great aspect is their relatively innocuous profile. However, up to one-third of patients develop antibodies during the 1st year of therapy with a subsequent reduction in effect.[10] Glatiramer is believed to act through tolerance induction of myelin-reactive lymphocytes.[11] These first-line MS platform therapies, known as disease-modifying therapies (DMTs), have the potential to alter the natural history of MS by reducing the frequency and severity of relapses, reducing the number of new and enlarging brain lesions on MRI, and slowing disability progression. Injectable DMTs are indicated for continuous use. As anesthesia and surgery in MS patients may cause exacerbations or exacerbations of the disease, attention should be paid to the application of anesthesia.[3] In MS, all anesthetic techniques may cause exacerbation in the symptoms. It has been reported that general anesthesia and low-dose local anesthesia and epidural anesthesia can safely be given, but the use of regional anesthesia is controversial.[3] Hypotension due to sympathetic blockade is severe when the autonomic nervous system is affected by MS. IV or inhaled anesthetic agents do not have any superiority to each other in patients with MS.[4] Neuromuscular-blocking drugs (NMBDs) should be used cautiously. Muscle relaxation level should be carefully monitored intra- and postoperatively. It must also be awake in terms of postoperative residual curarization in MS with general anesthesia patients. Exact monitoring of muscle relaxation is essential for proper use of muscle relaxants and to prevent postoperative residual paralysis.[12] Train-of-four (TOF) monitoring and single twitch (ST) stimulation of peripheral nerves are often used to monitor the degree of NMB when anesthetic techniques include the use of NMB agents (NMBAs). Using ST should establish a control value before the administration of NMBAs. ST and first twitch of TOF (T1) forces do not differ when employing a stimulus interval of 10 s or more.[12] The T1 response represents the effects of NMBAs in the postsynaptic membrane, while the TOF ratio (T4/T1, TOFR) shows the effect on the presynaptic membrane of the neuromuscular junction.[13] During spontaneous or pharmacologically induced offset of NMB, a TOFR of 0.9 has been reported to exclude clinically important residual NMB.[13] The T1 usually recovers at a rate similar to or faster than the TOFR after the reversal of competitive NMBAs by neostigmine. After reversal with the optimum dose of sugammadex during rocuronium-induced NMB, the time to 0.9 of the TOFR is much faster than that to 90% of T1 (T1/control value). A TOFR of 0.9 cannot assure adequate recovery of neuromuscular function in several minutes after sugammadex administration, if the T1 was not recovered completely.[14] Sugammadex binds with a high affinity to rocuronium or vecuronium in the blood, decreasing its plasma concentration and creating a gradient between the plasma and the neuromuscular junction. This process results in removing the nondepolarizing agent from the receptors as it follows the concentration gradient toward the blood.[15] Sugammadex, if given in appropriate doses, has the ability to reverse the effect of rocuronium more rapidly and effectively than neostigmine, especially from deeper levels of NMB.[16] It is known that MS may show different responses to muscle relaxants in the normal population. For this reason, in this study, we planned to measure TOF values of muscular strengths before and after anesthesia in patients undergoing general anesthesia in our hospital's operating theater.

## Materials and Methods

A prospective descriptive study of twenty cases was conducted over 2 years at the University of Health Sciences Bagcilar Training and Research Hospital. With the approval of the local ethics committee of the University of Health Sciences Bagcilar Training and Research Hospital and with written consent of participants, we anesthetized ten American Society of Anesthesiologists (ASA) I-III patients (from April 2014 to March 2017) with MS and ten ASA I-II patients without MS. Inclusion criteria were as follows: ten MS-diagnosed patients who underwent operations under general anesthesia (GA) with rocuronium and sugammadex as NMB reversal agent and as a control group we recruited ten ASA I-II patients without MS. Exclusion criteria were as follows: allergy to any agent used for anesthesia induction and maintenance, use of drugs that might interact with NMBAs, pregnancy, and a history of serious liver or kidney disease. GA was administered to all patients without premedication, starting with propofol (2 mg/kg) and fentanyl analgesia, 1 μg/kg. This was followed by inducing muscle relaxation with rocuronium of 0.6 mg/kg intravenously for orotracheal intubation. GA was supplemented in all patients by the inhalation of $O_2$ + air + sevoflurane (up to 2.0% in the expired mixture). Maintenance of NMB was performed with rocuronium relaxant (25% the initial dose) on those who showed recovery from block (emergence of two responses in TOF). All patients were monitored

with electrocardiogram, oxygen saturation, noninvasive blood pressure, and monitoring of NMB was done by an accelerometry (TOF watch). The electrodes were placed over the ulnar nerve near the wrist. The distal black (negative) electrode was placed near the wrist crease and the proximal red (positive) electrode was placed 3–6 cm proximal to the black electrode along the path of the ulnar nerve. Neuromuscular conduction was assessed by the acceleromyometric method using a TOF-Guard apparatus (Organon, Holland). After the last dose of rocuronium, at reappearance of second twitch, a single IV dose of sugammadex 2 mg/kg administered for reverse NMB. All doses of NMBAs and reversal agents were administered based on actual body weight. The patients were extubated after recovery of TOF higher than 0.9. The primary efficacy variable was the time from the start of administration of sugammadex to recovery of the TOFR to 0.9.

### Statistical analysis

Statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. Descriptive statistical methods (mean and standard deviation) were used in the evaluation of the data as well as independent *t*-test for the comparison of binary groups and Chi-square test for comparison of qualitative data. The results were evaluated at a significance level of $P < 0.05$. In the power analysis performed with the G* power 3.1 program related to our study, the presence of MS patients in the control and study groups was found between 2% and 24%[17] (alpha error probability = 0.05); with power value of 0.8, the number of samples required for each group was found to be ten in the sample width analysis.

## Results

There was no statistically significant difference between the mean age and gender distributions of MS and control groups ($P > 0.838$. $P = 1$). There was no statistically significant difference between ASA and operation distributions of MS and control groups ($P > 0.05$). There was no statistically significant difference between the Temp./°C averages of the operation room of MS and control groups ($P = 0.286$).

There was no statistically significant difference between anesthesia/min averages of MS and control groups ($P = 0.936$). There was no statistically significant difference between operation/min averages of MS and control groups ($P = 0.88$). There was no statistically significant difference between rocuronium/mg averages of MS and control groups ($P = 0.713$). There was no statistically significant difference between the MS and control groups' time to TOF >90/s averages ($P = 0.068$).

**Table 1: Demographic Data and Some Anesthetic Characteristics of the Partipicants**

| | MS Group ($n$=10), $n$ (%) | Control Group ($n$=10), $n$ (%) | $P$ |
|---|---|---|---|
| Age | 36.6±5.84 | 37.1±4.89 | 0.838 |
| Gender | | | |
| Male | 2 (20.00) | 2 (20.00) | 1 |
| Female | 8 (80.00) | 8 (80.00) | |
| ASA | | | |
| I | 1 (10.00) | 5 (50.00) | 0.113 |
| II | 8 (80.00) | 5 (50.00) | |
| III | 1 (10.00) | 0 (0.00) | |
| BMI | 27.92±1.99 | 28.23±1.52 | 0.7 |
| Operating room temperature/°C | 21.48±0.56 | 21.22±0.5 | 0.286 |
| Operation | | | |
| Appendectomy | 2 (20.00) | 2 (20.00) | 1 |
| Laparoscopic cholecystectomy | 5 (50.00) | 5 (50.00) | 1 |
| Laparoscopic ovarian cystectomy | 1 (10.00) | 1 (10.00) | 1 |
| Ovarian cystectomy | 1 (10.00) | 1 (10.00) | 1 |
| Total laparoscopic hysterectomy | 1 (10.00) | 1 (10.00) | 1 |
| Anesthesia/min | 77.5±43.92 | 76±38.86 | 0.936 |
| Operation/min | 69±40.4 | 66.5±36.9 | 0.887 |
| Rocuronium/mg | 60.5±13.22 | 58.5±10.55 | 0.713 |
| Time to TOF >90/s | 122±16.87 | 109±12.87 | 0.068 |

BMI=Body mass index; ASA=American Society of Anesthesiologists; TOF=Train of four

Demographic characteristics of the patient, operating room temperature, type of operation performed, duration of anesthesia and operation, NMB dose applied, time of TOF normalization, and *P* values are shown in Table 1.

## Discussion

To our knowledge, this study is the first controlled trial in which for MS patients, TOF monitoring and sugammadex were used together. Optimal anesthetic care of MS patients entails detailed preoperative evaluation, medication history, and neurologic examination, trying to prevent conditions such as fever, stress that may precipitate attacks, as well as postoperative attention to respiratory risk factors.[4] The main concern is disease exacerbation and MS attacks following anesthesia and surgery. Elevated body temperature is one of the most studied triggers.[3] In our study group and patients in the control group, we escaped from high temperature. The mean temperature of the operation chamber was 21.48°C ± 0.56°C and 21.22°C ± 0.5°C in the MS and control groups, respectively. The variable degree of hemodynamic instability is also important for the anesthetists.[3] Literatures regarding anesthetic management of MS patients include the use of GA,

spinal, and epidural techniques. We decided to use GA, because all operations were requiring abdominal surgery. There are several reports of successful usage of sevoflurane in MS patients;[18,19] therefore, sevoflurane was also our choice for the maintenance of anesthesia. Special attention is also required with the use of NMBDs. In patients with MS, an upregulation of nicotinic acetylcholine receptors of skeletal muscles is noted. In addition, a constitutional change of the receptor subunits leading to prolonged duration of channel opening is seen.[3] Even though resistance to nondepolarizing NMBD has been reported in the past, it does not seem to occur very often as normal response has been described in several cases.[20] Due to the unpredictable response to nondepolarizing NMBDs, it is imperative to carefully arrange the dose administered. Neuromuscular monitoring preferentially in a nonaffected or the least affected limb is advised. It is known that drugs used in the treatment of MS, in particular glatiramer acetate, may change the anesthetic drug metabolism and clearance depending on hepatotoxicity.[21] Therefore, a longer than usual duration of muscle relaxation induced by rocuronium could be expected. It is also known that sevoflurane potentiated rocuronium-induced NMB.[22] For this reason, we applied TOF monitoring in our work. We also used sugammadex to reverse the effect of rocuronium in our patients, especially to prevent postoperative residual paralysis.[23,24] It was demonstrated in different trials that 2 mg/kg sugammadex decreases the mean time to recovery after rocuronium usage to 1.2–3.0 min.[25] After the last dose of rocuronium, at reappearance of second twitch, a single IV dose of sugammadex 2 mg/kg was administered to reverse NMB. All doses of NMBAs and reversal agents were administered based on the actual body weight. The patients were extubated after the recovery of TOF higher than 0.9. The primary efficacy variable was the time from the start of administration of sugammadex to recovery of the TOFR to 0.9. These durations were similar in both groups, 122 ± 16.87 and 109 ± 12.87 s, respectively. The operation and anesthesia durations are similar because the demographic characteristics of both groups, the ASAs, the type of operation applied, and the temperature of the operation rooms are similar. Anesthesia times of MS and control groups are 77.5 ± 43.92 and 76 ± 38.86 s, respectively. Operation times of MS and control groups are 69 ± 40.4 and 66.5 ± 36.9 s, respectively. Similar characteristics of both groups were of concern for postoperative residual paralysis, and therefore we did not notice any difference between time to TOF >90/s for both groups. There was no statistically significant difference between the MS and control groups' time to TOF >90/s averages ($P$ = 0.068). A statistically insignificant difference between the two groups did not remove our concerns about general anesthesia in patients with MS. General anesthesia with MS patients has some risk of postoperative residual curarization. Studies with general anesthesia for MS patients should be done in larger patients groups and more studies on this subject should be done.

## Conclusion

We could not meet with the postoperative risks due to the fact that the patient's temperature, the NMB, and the type of anesthesia were uneventful. TOF monitoring and sugammadex prevented postoperative residual paralysis in our practice. The use of TOF monitoring and sugammadex during general anesthesia in MS is very important for reducing perioperative risks and eliminating postoperative residual paralysis. Sugammadex could be used safely and effectively in MS patients. Sugammadex and TOF patients will increase patient safety in general anesthesia practice.

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### Conflicts of interest

There are no conflicts of interest.

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