Use of sugammadex in patients with neuromuscular disorders: a systematic review of case reports

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Abstract

Background: Sugammadex is a modified gamma-cyclodextrin that acts by selectively encapsulating free amino-steroidal neuromuscular relaxants. Several case reports have been published on the use of sugammadex in patients with neuromuscular disorders that include neuromuscular junction diseases, myopathies, neuropathies, and motor neurone disorders. The primary aim of this review is to systematically review the evidence on the use of sugammadex in patients with this heterogeneous group of diseases and provide recommendations for clinical practice.

Methods: A systematic electronic search of Medline, Embase and CINAHL databases was done until June 2019, to identify case reports describing the use of sugammadex in adult surgical patients with neuromuscular disorders.

Results: Of the 578 records identified through database searches, 43 articles were finally included for the systematic review. Of these, 17 reports were on patients with myopathy, 15 reports on myasthenia gravis, 9 reports on motor neuron diseases and 2 reports on neuropathies.

Conclusions: Majority of the articles reviewed report successful use of sugammadex to reverse steroidal muscle relaxants, especially rocuronium, in patients with neuromuscular diseases. However, with sugammadex, unpredictability in response and uncertainty regarding optimum dose still remain issues. Quantitative neuromuscular monitoring to ensure complete reversal and adequate postoperative monitoring is strongly recommended in these patients, despite the use of sugammadex.

Keywords: Sugammadex, Neuromuscular diseases, Rocuronium, Neuromuscular blockade, Reversal

Background

Neuromuscular disorders are a large heterogeneous group of diseases that are usually progressive and produce symptoms at widely differing age ranges with varying degrees of severity [1]. They can be classified into motor neuron diseases, neuropathies, neuromuscular junction disorders or myopathies depending on which section of neuromuscular system is affected [1] (Table 1). Epidemiological studies report an increase in the prevalence of neuromuscular disorders worldwide [2–4]. There have been several publications expressing concerns over the choice of muscle relaxants in patients with neuromuscular disorders presenting for surgery but perhaps, the reversal of the effects of muscle relaxants is a greater concern.

Sugammadex (Bridion®, Organon/Schering-Plough USA) a modified γ- cyclodextrin, acts by selectively encapsulating free molecules of amino-steroidal neuromuscular relaxants such as vecuronium and rocuronium forming 1:1 inclusion complex in the plasma, thereby creating a concentration gradient resulting in the reduction of the relaxant available at the neuromuscular junction [5–7]. The complex is pharmacologically inert, is not affected by acid-base status or temperature [8] and produces no hemodynamic changes [6]. Thus, sugammadex has been found to have a good safety profile so far, compared with neostigmine [9].

Due to its rapid onset of action, sugammadex has enabled rocuronium to be used in difficult intubation scenarios, where traditionally suxamethonium has been

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the relaxant of choice [10]. Sugammadex also permits the anesthesiologist to use high dose of rocuronium both for rapid sequence induction and intubation [11] as well as to ensure optimal surgical conditions, by enabling a complete motor recovery and reduced need for postoperative ventilatory support [12]. Moreover, the time taken by sugammadex to adequately reverse moderate to deep block has been found to be shorter than that for neostigmine [10]. Hence, the use of sugammadex is being increasingly reported in patients with neuromuscular disorders. However, synthesis of the evidence from these isolated case reports may provide a more meaningful guidance to the anesthesiologists with their management of such patients and to generate new research hypotheses.

The purpose of the following review is to evaluate the evidence supporting the use of sugammadex as a reversal agent in patients with neuromuscular disorders, in terms of its efficacy and dose requirements and to summarize various aspects that need to be considered during administration of this drug. A detailed review of neuromuscular diseases and their anesthetic considerations is outside the scope of this article.

Methods
A search was done by the reviewers (U.G and L.S) in Medline, Embase and CINAHL using the key Medical Subject Headings (MeSH) terms, “sugammadex”, “neuromuscular diseases”, “neuromuscular junction disorders”, “myopathy”, “neuropathy”, “hereditary motor sensory neuropathy”, “motor neuron disease”, “neuromuscular transmission disorders”, “Neuromuscular blocking” for studies including case reports on adult humans, and published in peer-reviewed journals, without any restriction on the year of publication. The last search was on 24 June 2019. Adult surgical patients with all variants of neuromuscular diseases who received sugammadex for reversal were eligible for inclusion. Paediatric case reports were excluded. Conference abstracts without full text availability and the articles that were not in English were excluded. Controlled trials on sugammadex, studies that did not use neuromuscular monitoring or did not report train-of-four ratio (TOF ratio) or count (TOF count) were excluded. Authors were not contacted for additional information. Duplicates were removed. Full texts of the articles from the relevant abstracts were reviewed. The reference list of the articles thus obtained was manually searched for any additional relevant article by L.S.

Two reviewers (U.G and S.K) independently screened the title and abstracts of all the articles from the literature search to select articles for full-text review with the inclusion and exclusion criteria. Any discrepancy was resolved by mutual consensus and discussion with the reviewer (L.S). Data were extracted by U. G and S. K into an excel sheet and included author, year, country, patient details, nature of disease, type of surgery, duration of surgery, anesthetic agents, neuromuscular blocking agent and its dose, neuromuscular monitor used, dose of sugammadex and its response and postoperative course. Details of the selection process are given in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Fig. 1).

Results
The search identified 578 citations, 72 relevant abstracts were screened, from which 29 articles excluded, leaving 43 articles suitable for review (Fig. 1). There were 22 publications from Europe, 15 publications from Asia and five from Australia. The maximum number of reports (n = 17) concerned patients with myopathies, followed by patients with myasthenia gravis (n = 15). One Australian paper [13] reported two cases, of which one concerned a patient with myotonic dystrophy and the other about a patient with spinal muscular atrophy. For the sake of classification, it was considered as two different reports. Two reports were on patients with neuropathies and nine on motor neuron diseases.

Discussion
Respiratory involvement in neuromuscular disorders can range from a reduction in inspiratory and expiratory muscle strength resulting in alveolar hypoventilation, poor clearance of airway secretions to atelectasis and respiratory failure1. There may be coexisting mild to moderate bulbar dysfunction increasing risk of aspiration and obstructive and central sleep apnea [14]. Hence, muscle relaxants have been cautiously or even sparingly used in patients with neuromuscular disorders in order to avoid the need for postoperative ventilatory support. However, inadequate relaxation due to restricted use of muscle relaxants can compromise the success of some abdominal and gynecological procedures [15, 16]. Use of suxamethonium in patients with neuromuscular disorders may risk patients with neuromuscular disorders have a high risk of postoperative respiratory complications including respiratory failure.

Table 1 Classification of the neuromuscular disorders
1. Neuromuscular transmission disorders: Myasthenia Gravis, Lambert-Eaton syndrome.
2. Myopathies: Muscular dystrophies including myotonias- dystrophic and non-dystrophic myotonias, poly- and dermatomyositis, metabolic and mitochondrial myopathies.
3. Neuropathies: Inflammatory polyneuropathy (Guillain – Barré syndrome), hereditary and toxic polyneuropathy (Charcot-Marie-Tooth disease, Fredreich’s ataxia), multiple sclerosis and mitochondrial myopathies.
4. Motor neuron diseases: Amyotrophic lateral sclerosis, spinal muscular atrophy, spinal bulbar muscular atrophy.
them with its undesirable side effects such as myalgia, malignant hyperthermia, decreased heart rate, masseter spasm, anaphylaxis, increased intracranial and intraocular pressure, hyperkalemia and prolongation of neuromuscular block in patients with congenital or acquired variations in plasma cholinesterase activity [17, 18]. The response and duration of action of rocuronium can be variable and unpredictable in these patients [19]. Since patients with neuromuscular disorders may also have other associated conditions such as cardiomyopathy [20], systemic and pulmonary hypertension and arrhythmias, the conventional combination of reversal agents (neostigmine and anticholinergic drugs) may cause cardiac rhythm disturbances. Previous case reports have also described prolonged neuromuscular blockade similar to depolarizing block or a tonic response following the use of neostigmine in patients with neuromuscular disorders [21]. Other drawbacks of anticholinesterases such as neostigmine include relatively slow onset along with questionable reliability and predictability of reversal [22].

A recent Cochrane review concluded that sugammadex is faster, more efficient and safer than neostigmine in reversing moderate and deep paralysis [23]. Within our literature search, evidence was collected on the use of sugammadex in four main types of neuromuscular disorders:

**Neuromuscular transmission disorders (Table 2)**

Myasthenia gravis is a common autoimmune disorder that can manifest as muscle weakness that is either generalized or isolated to ocular/bulbar muscles. It may also be associated with autonomic instability. Dosing of muscle relaxants may pose challenges in patients with myasthenia gravis. They could be resistant to suxamethonium with up to twice-normal ED_{50} values, with increased risk of phase II blockade at higher doses [24].

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2Sugammadex should be strongly considered as a safer and effective alternative to neostigmine in the reversal of steroidal muscle relaxants.
| Author/year | Country | Patient characteristics | Disease Type | Duration of surgery | Anesthetic agents | NMBA | NM monitoring | Dose of sugammadex & results of NM monitor | Postoperative course |
|-------------|---------|-------------------------|--------------|---------------------|------------------|------|--------------|------------------------------------------|---------------------|
| de Boer et al., 2010 | Netherlands | 2 patients- details not provided | Myasthenia gravis | Short procedures - details not provided; N.R. | N.R. | Rocuronium 0.15 mg/kg | Acceleromyography (TOF-Watch SX) | Sugammadex 4 mg/kg; Pre reversal TOF count: 0 & PTC: 0; Post reversal TOF ratio: 0.9 (2.7 min for the first patient & 2.25 min for the second patient) | Uneventful extubation and recovery |
| Petrun et al., 2010 | Slovenia | 44/F; 55 kg, 153 cm; BMI: 23.5 kg/m² | Myasthenia gravis | Laparoscopic cholecystectomy; around 30 min | Propofol, sufentanil induction followed by maintenance with sevoflurane/oxygen/air | Rocuronium 0.36 mg/kg, then 0.18 mg/kg | Acceleromyography (TOF watch 5) | Sugammadex 2 mg/kg; Pre reversal TOF ratio: 0.23; Post reversal TOF ratio: 1.4 (4 min) | Uneventful extubation and recovery |
| Unterbuchner et al., 2010 | Germany | 72/M; 88 kg, 172 cm; BMI: 29.7 kg/m² | Myasthenia gravis | Elective radical prostatectomy; 210 min | Propofol, sufentanil induction followed by maintenance with propofol infusion and sufentanil bolus | Rocuronium 22 mg initial bolus and another 21 mg before intubation; followed by rocuronium infusion (cumulative rocuronium dose: 151 mg) | Electromyography (NM transmission module in GE Datex Light Monitor) | Sugammadex 2 mg/kg; Pre reversal TOF count: 2; Post reversal TOF ratio: 0.9 (3.5 min) | Uneventful extubation and recovery in the intermediate care unit |
| Argiriadou et al., 2011 | Greece | 31/F; 95 kg/160 cm; BMI: 37 kg/m² | Myasthenia gravis | Transternal thymectomy; 70 min | Propofol, fentanyl induction followed by propofol infusion | Rocuronium 0.5 mg/kg; no further dose | Acceleromyography (TOF-Watch SX) | Sugammadex 2 mg/kg; Pre reversal TOF ratio: 0.3; Post reversal TOF ratio: 0.92 (3 min), 1.02 (7 min) | Uneventful extubation and recovery |
| Mitre et al., 2011 | Romania | 56/F; 90 kg, 179 cm; BMI: 28.1 kg/m² | Myasthenia gravis | Laparoscopic cholecystectomy; 40 min | Thiopentone, midazolam and fentanyl induction followed by maintenance with sevoflurane/oxygen/air | Rocuronium 0.6 mg/Kg | Acceleromyography (TOF-Watch SX) | Sugammadex 2 mg/kg; Pre reversal TOF ratio: 0.67; Post reversal TOF ratio: 0.96 (1 min) | Uneventful extubation and recovery |
| Garcia et al., 2012 | France | 35/F; 80 kg; 34 weeks gestation | Myasthenia gravis | Emergency cesarean section; 90 min | Propofol, sufentanil induction followed by maintenance with propofol infusion | Rocuronium 8 mg (0.15 mg/kg), modified rapid sequence induction | Qualitative neuromuscular monitoring | Sugammadex 200 mg (4 mg/kg ideal body weight); Pre reversal TOF count: 1; Post reversal TOF count: 4 (4 min) | Artificial ventilation for 48 h due to failure to wean despite good motor response |
### Table 2: Summary of case reports on the use of sugammadex in patients with myasthenia gravis (n = 15) (Continued)

| Author/year | Country | Patient characteristics | Disease Type | Type of surgery; Duration of surgery | Anesthetic agents | NMBA | NM monitoring | Dose of sugammadex & results of NM monitor | Postoperative course |
|-------------|---------|-------------------------|--------------|--------------------------------------|-------------------|------|---------------|--------------------------------------------|---------------------|
| Jakubiak et al., 2012 | Poland | 38/F; 160 kg/181 cm; BMI: 48.8 kg/m² | Myasthenia gravis | Elective laparoscopic adjustable gastric banding; 42 min | Propofol total intravenous infusion | Rocuronium 24 mg (0.15 mg/kg) | Acceleromyography | Sugammadex 200 mg (2 mg/kg corrected body weight); Pre reversal TOF count: 1; Post reversal TOF ratio: 1 (2.8 min) | Uneventful extubation and recovery in both the cases |
| Üstün et al., 2012 | Turkey | 2 adult patients: Case 1: 55/F; BMI 37 kg/m²; Case 2: 45/F, BMI 27 kg/m² | Myasthenia gravis | Case 1: Disc Hernia repair; 135 min Case 2: Abdominal hysterectomy; 96 min | Propofol, remifentanil induction followed by maintenance with remifentanil infusion and sevoflurane/oxygen/air | Case 1: Rocuronium 0.2 mg/kg for intubation followed by 1/8th of the dose as top up Case 2: Rocuronium 0.25 mg/kg | Acceleromyography (TOF-Watch SX®) | Case 1: Sugammadex 2 mg/kg; Pre reversal TOF ratio: 0.15; Post reversal TOF ratio: 1 (2 min) Case 2: Sugammadex 2 mg/kg; Pre reversal TOF count: 2; Post reversal TOF ratio: 1 (5 min) | Uneventful extubation and recovery |
| Iwasaki et al., 2013 | Japan | 2 patients. Case 1: 74/F; 54 kg/157 cm; BMI: 21.9 kg/m²; Case 2: 71/M, 72 kg/165 cm; BMI: 26.4 kg/m² | Ocular myasthenia gravis | Case 1: Capsulosynovectomy left elbow: N.R. Case 2: Transcervical thymectomy; N.R. | Case 1: Propofol induction followed by maintenance with propofol and remifentanil Case 2: Propofol induction followed by maintenance with sevoflurane, remifentanil along with epidural anaesthesia (T5-T6 level) | Case 1: Rocuronium 0.5 mg/kg; additional 0.2 mg/kg if TOF count ≥ 2 Case 2: Rocuronium 0.3 mg/kg; additional 0.15 mg/kg if TOF count ≥ 2 | Acceleromyography (TOF-Watch SX®) | Case 1: Sugammadex 2 mg/kg followed by two additional boluses of 1 mg/kg; Pre reversal TOF ratio: 0.2; Post reversal TOF 0.9 (1.5 min); Subsequently two additional boluses of 1 mg/kg sugammadex were administered Case 2: Sugammadex 1 mg/kg followed by two additional boluses of 1 mg/kg; Pre reversal TOF count: 2; Post reversal TOF ratio 0.9 (6.5 min) (after 2 mg/kg sugammadex) | Uneventful extubation and recovery |
| Kiss et al., 2013 | Switzerland | 25/F; BMI: 32.0 kg/m² | Myasthenia gravis | Thymectomy; 120 min | Propofol infusion and sufentanil | Rocuronium 30 mg for intubation along with two 10 mg boluses (total 50 mg) | Datex Ohmeda M-NMT module and portable neuromuscular stimulator | Total dose of sugammadex: 17.34 mg/kg; Pre reversal TOF ratio: 0.36, Post reversal TOF ratio: 0.71 (after more than 8 min). | Pyridostigmine was given through nasogastric tube. Extubation after long waiting time, at the end of surgery |
Table 2  Summary of case reports on the use of sugammadex in patients with myasthenia gravis (n = 15) (Continued)

| Author/year | Country | Patient characteristics | Disease | Type of surgery; Duration of surgery | Anesthetic agents | NMBA | NM monitoring | Dose of sugammadex & results of NM | Postoperative course |
|-------------|---------|-------------------------|---------|--------------------------------------|------------------|------|--------------|---------------------------------|---------------------|
| Sugi et al., 2013 | Japan | 26 yr/f; 64 kg; 165 cm | Myasthenia gravis | Extended thymectomy; 155 min | Induction and maintenance with TCI propofol and remifentanil infusion supplemented with fentanyl boluses | Rocuronium 6 mg (0.09 mg/kg) for intubation; Total dose of rocuronium 28 mg. | Acceleromyography (TOF-Watch SX®) | Sugammadex 2 mg/kg. Post reversal TOF ratio: 0.55 (85 min). Additional 2 mg/kg sugammadex administered: No change in TOF ratio. Further supplemented with neostigmine 0.3 mg/kg. Post neostigmine TOF ratio: 0.86 (5 min). Post reversal TOF ratio (3 h & 7 h): 0.8 & 0.9 respectively. | Extubated after a delay at the end of surgery; Uneventful recovery |
| Sungur Ulke et al., 2013 | Turkey | 10 patients: mean age: 31 ± 12 years; Weight: 68 ± 13 kg | Myasthenia gravis | Video thoracoscopic assisted thymectomy; mean surgical time: 62 +/- 16 min | Propofol, Fentanyl induction followed by propofol infusion & fentanyl boluses | Rocuronium 0.3 mg/kg. Mean total dose of rocuronium: 48 +/- 16 mg | Acceleromyography (TOF-Watch S®) | Sugammadex 2 mg/kg; Pre reversal TOF ratio: ranged from 0 to 0.5; Mean time to TOF > 0.9: 1.85 min. | Uneventful extubation and recovery |
| Casarotti et al., 2014 | Italy | 2 patients: Case 1: 48/M; BMI: 32.7 kg/m². Case 2: 71/F | Myasthenia gravis | Case 1: Emergency laparotomy; 120 min Case 2: Emergency endoscopy for hemostasis; 60 min | Propofol, remifentanil induction followed by maintenance with propofol and remifentanil infusion | Case 1: Rocuronium 1.2 mg/kg ideal body weight. Rapid sequence induction Case 2: Rocuronium 1 mg/kg ideal body weight Rapid sequence induction | Acceleromyography (TOF-Watch SX®) | Case 1: Sugammadex 4 mg/kg actual body weight. Pre reversal PTC > 1. Post reversal TOF ratio: 0.9 (3 min) Case 2: Sugammadex 4 mg/kg actual body weight. Pre reversal TOF count: 1; Post reversal TOF ratio: 1 (2 min) | Intensive care unit monitoring; sedated for at least 30 min after sugammadex and then extubated; uneventful recovery |
| de Boer et al., 2014 | Netherlands, UK | 21 patients; M: 8; F: 13. Mean age 56 years Average weight 77.6 kg | Myasthenia gravis | Thymectomy: 10 Breast surgery: 3; Laparoscopic cholecystectomy: 1; Urological surgery: 2; Craniotomy: 1; Laminectomy: 1; Inguinal hernia repair: 1; Gastric surgery: 1; Skin lesions: 1; Duration: N.R. | Propofol, remifentanil induction and maintenance or propofol induction and sevoflurane for maintenance | Rocuronium: 13 patients: 0.1–1.0 mg/kg; Vecuronium: 8 patients: 0.1–0.2 mg/Kg | Acceleromyography (TOF-Watch SX®) a) Sugammadex 2 mg/kg for 12 patients. Pre reversal TOF count: 21 response; Post reversal TOF ratio: 0.9 (1.3 min) b) Sugammadex 4 mg/kg for 9 patients. Pre reversal TOF count: 0. Post reversal TOF | Uneventful extubation and recovery in all patients. |
| Author/year, Country          | Patient characteristics | Disease               | Type of surgery; Duration of surgery                        | Anesthetic agents                        | NMBA | NM monitoring                        | Dose of sugammadex & results of NM monitor | Postoperative course            |
|----------------------------|-------------------------|-----------------------|----------------------------------------------------------------|------------------------------------------|------|-------------------------------------|-------------------------------------------|------------------------------------------|
| Vymazal, Czech Republic     | 117 patients; M: 67, F: 50; Mean age: 41.6 years; Mean BMI: 24.2 kg/m² | Myasthenia gravis     | 105 patients: Surgical thymectomy, 12 patients: cholecystectomy; mean surgical time: 98.6 min | Propofol, sufentanil boluses; isoflurane/oxygen/air | Rocuronium 0.6 mg/kg for intubation with additional boluses of 0.15 mg/kg if required; Total dose of rocuronium: 72.5 mg. | Acceleromyography (TOF-Watch SX) | Sugammadex 2 mg/kg (if pre reversal TOF count: 2/2) or 4 mg/kg (if pre reversal TOF count: 0-1); Post reversal TOF ratio: 0.9 (average 1.95 min) | Uneventful extubation and recovery |

*Results at the adductor pollicis muscle

TOF Train of four, PTC Post tetanic count, N.R. Not reported, NMBA Neuromuscular blocking agent, NM Neuromuscular

Table 2 Summary of case reports on the use of sugammadex in patients with myasthenia gravis (n = 15) (Continued)
contrast, patients with myasthenia gravis are sensitive to non-depolarizing relaxants due to a decreased number of acetylcholine receptors and hence a dose reduction of these drugs has been recommended [25–27]. In the studies reviewed, the bolus intubating dose of rocuronium used in the patients with myasthenia gravis ranged from 0.09–1.2 mg/kg. Factors such as the use of pyridostigmine and its dose may also impact on the effects and the duration of non-depolarising agents [28]. Moreover, since the acetylcholine esterase is already inhibited by pyridostigmine, reversing residual block with neostigmine may not be fully effective [24, 25, 27]. Use of sugammadex can provide fast and reliable recovery irrespective of preoperative continuation or cessation of pyridostigmine [29]. A large retrospective cohort study has shown a significant reduction in myasthenic crisis and hospital costs following surgery when sugammadex was used [30].

In the literature reviewed, the documented dosing of sugammadex was also found to vary between reports (Table 2). A dose of 2 mg/kg sugammadex has been noted to be sufficient even with a TOF count of 0 at the time of administration [31] whereas a dose of 4 mg/kg has been used by other authors [29, 32]. In the largest case series to date on the use of sugammadex in myasthenic patients, administration of sugammadex at 2 or 4 mg/kg depending on a TOF count to ≥2 or 0–1 respectively, resulted in full reversal with a duration of less than 2 min on average [33]. However, as per the other reports in our review, complete reversal of relaxant effect occurred within around 3–4 min following sugammadex administration. Interestingly, four reports [32, 34–36] describe persistent residual paralysis in patients with myasthenia gravis even after administration of sugammadex. Kiss et al. [34] described the persistence of neuromuscular blockade in a patient with myasthenia gravis, resulting in the administration of a total dose more than 16 mg/kg, in addition to administration of pyridostigmine via nasogastric tube. This was attributed to both redistribution of muscle relaxant and artifact from neuromuscular monitors. Surgery-induced exacerbation of myasthenia gravis has also been noted to result in residual paralysis despite a sugammadex dose of 4 mg/kg [32, 35].

In terms of monitoring the adequacy of reversal, motor recovery can occur later at the corrugator supercilii muscle (CSM) than at the adductor pollicis muscle (APM) in patients with ocular myasthenia as opposed to individuals without the disease [37]. In addition, recovery of TOF ratio may be faster than that of first twitch (T1) height after sugammadex administration as observed by Iwasaki et al. in two patients with myasthenia gravis. While the TOF ratio at the APM returned to 90% within 1.5 min and 6.5 min in their two patients, T1 recovery took up to 12 min and 13 min respectively and required additional doses of sugammadex. Hence the authors recommended monitoring TOF ratio as well as the recovery of T1 height to baseline at both APM and CSM, in patients with myasthenia gravis [37]. However, recovery of TOF ratio was found to lag behind T1 recovery in the case reported by Sugi et al. [35].

Myopathies (Table 3)
Muscular dystrophies are a heterogeneous group of progressive neuromuscular disorders resulting from genetic mutations that cause dystrophic changes in muscles. The most common varieties are Duchenne, Becker and myotonic dystrophies [38]. Patients suffer varying patterns of skeletal muscle weakness depending on the mutation, cardiac abnormalities including cardiomyopathies with or without conduction defects and are prone to pulmonary infection and failure. Myotonic dystrophy is also characterized by prolonged contraction of muscle with defective relaxation. Renal dysfunction may be a common complication in patients with myotonic dystrophy [39]. Patients with myotonic dystrophy tend to show myotonic responses to suxamethonium [40] and increased sensitivity to non-depolarising muscle relaxants [41]. Reactions to neostigmine can also be unpredictable [21, 41]. None of these reactions were observed by Imison et al. in the retrospective study on myotonic dystrophy patients [42].

Ten reports discussed the use of sugammadex patients with myotonic dystrophy and two reports in patients with Becker and Duchenne muscular dystrophy [20, 43] (Table 3). The dose of rocuronium have been very variable with these studies. Reduced doses (<0.6 mg/kg) of rocuronium have been administered to aid intubation in majority of the cases in our review [13, 20, 43–49]. With these cases, the reversal times to TOF ratio of 0.9 with 2 mg/kg sugammadex ranged from 2 min [20, 45, 46] to 5 min [13, 44, 48]. However, two authors have

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3Reduced dose of rocuronium has been used in these patients while the standard recommended dose of sugammadex has been successfully used to reverse muscle relaxants in the majority of the published case reports.

4Variations from normal recovery patterns of muscle strength following administration of reversal agent have been observed in patients with neuromuscular diseases. In myasthenia gravis especially in ocular myasthenia, both spontaneously and with administration of sugammadex, earlier recovery of TOF ratio versus first twitch height and earlier recovery at corrugator supercilii muscle versus adductor pollicis muscle were observed. Hence, monitoring TOF ratio as well as the recovery of first twitch height to baseline at both the muscles is recommended.
| Author/year          | Country  | Patient characteristics | Disease              | Type of surgery; Duration of surgery | Anesthetic agents                                                                 | NMBA          | NM monitoring                      | Dose of sugammadex & results of NM monitor | Postoperative course                           |
|---------------------|----------|--------------------------|----------------------|---------------------------------------|-----------------------------------------------------------------------------------|---------------|-------------------------------------|---------------------------------------------|---------------------------------------------|
| Baumgartner, 2010   | Australia| 59/M; 75 kg              | Classic severe myotonic dystrophy | Elective laparoscopy; 46 min          | Propofol, alfentanil for induction followed by maintenance with fentanyl boluses | 30 mg (0.4 mg/kg) rocuronium given after intubation | Qualitative neuromuscular monitoring | Sugammadex 150 mg; Pre reversal TOF count: 0 with myotonic response to tetany; Post reversal TOF count: 4 equal twitches (4 min) | Extubated end of surgery (within 10 min of sugammadex dose) |
| Matsuki, Y et al., 2011 | Japan    | 24/F; 75 kg; 160 cm.     | Myotonic dystrophy   | Laparoscopic ovarian cystectomy; N.R. | Propofol, remifentanil induction followed by maintenance with propofol, remifentanil infusion | Rocuronium 0.3 mg/kg followed by 0.1 mg/kg with the appearance of 4th twitch | Acceleromyography (TOF-Watch SX®) | Sugammadex 2 mg/kg; Pre reversal TOF count: 2; Post reversal TOF: 0.9 (< 2 min) | Extubation at the end of surgery             |
| Mavridou et al., 2011 | Greece   | 40/F; 74 kg; 160 cm; BMI: 28.9 kg/m² | Myotonic dystrophy | Laparoscopic cholecystectomy and right ovarian cystectomy; 90 min | Propofol induction followed by propofol, remifentanil infusion with oxygen/air | Rocuronium 30 mg (0.4 mg/kg) | Acceleromyography (TOF-Watch SX®) | Sugammadex 2 mg/kg; Pre reversal TOF count: 2; Post reversal TOF ratio: 1.0 (2 min) | Mechanically ventilated for around 25 min due to pethidine-induced respiratory depression, which was reversed with naloxone; Uneventful extubation; No complications thereafter. |
| Petrovski, 2011     | Australia| 43/F; BMI: 55 kg/m²       | Myotonic dystrophy   | First surgery: Cystoscopy & colonoscopy; 90 min Second surgery: urological procedure; 180 min | First surgery: Propofol and sevoflurane/oxygen induction followed by maintenance with desflurane/oxygen/air with fentanyl. Second surgery: Details not reported, other than 200 mcg fentanyl | First surgery: Rocuronium 50 mg for intubation; Second surgery: Rocuronium 50 mg + Cisatracurium 4 mg | Qualitative neuromuscular monitoring | First surgery: Pre reversal TOF count 4; Sugammadex 200 mg; Post reversal TOF: N.R. Second surgery: Pre reversal TOF count:4; Reversal with Neostigmine 2.5 mg & Glycopyrollate 0.4 mg; Post reversal TOF: strong 4 twitches, however clinical signs of inadequate muscle strength recovery | First surgery: Uneventful extubation; Second surgery: Failed extubation, requiring 3 h of ventilation and postoperative lung infection. |
| Suzuki et al., 2012 | Japan    | 75 yr/M                  | Dermatomyositis      | Open reduction of fracture elbow; 25 min | Propofol, fentanyl induction followed by maintenance with sevoflurane, remifentanil infusion and fentanyl boluses | Rocuronium 0.6 mg/kg | Acceleromyography (TOF-Watch SX®) | Sugammadex 2 mg/kg; Pre reversal TOF count: 1; Post reversal TOF: 0.9 (5.75 min) | Uneventful extubation and recovery           |
Table 3 Summary of case reports on the use of sugammadex in patients with myopathies (n = 17) (Continued)

| Author/year | Country       | Patient characteristics | Disease                        | Type of surgery; Duration of surgery | Anesthetic agents                                                                 | NMBA   | NM monitoring                                           | Dose of sugammadex & results of NM monitor | Postoperative course |
|------------|---------------|-------------------------|---------------------------------|-------------------------------------|----------------------------------------------------------------------------------|--------|--------------------------------------------------------|---------------------------------------------|----------------------|
| Kashiwai et al., 2012 | Japan | 37/F; 55 kg; 154 cm | Myotonic dystrophy | Open resection of ovarian tumor | General anesthesia with fentanyl and propofol target-controlled infusion followed by maintenance with propofol, remifentanil infusions and intermittent epidural ropivacaine | Rocuronium 1 mg/kg followed by a subsequent bolus of 0.2 mg/kg | Acceleromyography (TOF-Watch SX*) | Sugammadex 2 mg/kg; Pre reversal TOF count: 2; Post reversal TOF: 0.9 (1.5 min) | Uneventful extubation and recovery |
| Carron et al., 2013 | Italy | 67/F; 60 kg; 155 cm; BMI: 25 kg/m² | Polymyositis with Sjogren’s syndrome | Laparoscopic sigmoid resection for diverticulitis; 210 min | Propofol, fentanyl induction followed by maintenance with desflurane and remifentanil | Rocuronium 0.9 mg/kg bolus followed by additional boluses to a total dose of 220 mg | Acceleromyography (TOF-Watch SX*) | Sugammadex 4 mg/kg; Pre reversal TOF count: 0; PTC: 1; Post reversal TOF ratio: 1.1(1.5 min) | Uneventful extubation and recovery |
| *Stewart et al., 2013 | Australia | 38/F; 76 kg; 165 cm; BMI: 27.9 kg/m² | Myotonic dystrophy | Laparoscopic cholecystectomy; 65 min | Propofol, remifentanil induction followed by maintenance with propofol and remifentanil infusion | Rocuronium 35 mg (0.47 mg/kg); Rapid sequence induction with orocoid pressure | Acceleromyography (M-NMT, Datex Ohmeda, Finland) | Sugammadex 200 mg (2.7 mg/kg); Pre reversal TOF count: 2; Post reversal TOF: 0.9 (5 min) | Uneventful extubation and recovery; Postoperative monitoring in intensive care unit |
| Stourac et al., 2013 | Czech Republic | 32/F; 38 weeks gestation | Myotonic dystrophy | Elective cesarean section; 55 min | Propofol induction followed by maintenance with sevoflurane | Rocuronium 1 mg/kg | Acceleromyography (TOF-Watch SX*) | Sugammadex 4 mg/kg; Pre reversal TOF count: 0; Post reversal TOF ratio: 0.9 (2 min) | Uneventful extubation and recovery |
| Wefki et al. Abdelgawwad Shousha et al., 2014 | Italy | 25/M; BMI: 25.6 kg/m² | Duchenne Muscular dystrophy | Open cholecystectomy; 240 min | Propofol, fentanyl induction followed by maintenance with sevoflurane/oxygen | Rocuronium 10 mg to facilitate rapid sequence intubation followed by 5 mg every 45 min, | Acceleromyography (TOF Guard) | Sugammadex 150 mg; Pre reversal TOF ratio: 0.25; Post reversal TOF ratio: 0.9 (10 min) | Uneventful extubation and recovery |
| Shimauchi et al., 2014 | Taiwan | 54/M; 54 kg; 167 cm; BMI: 19.4 kg/m² | Becker’s muscular dystrophy | Laparoscopic cholecystectomy; 92 min | Fentanyl, midazolam induction; maintenance with propofol, remifentanil infusion, oxygen/air | Rocuronium 20 mg (0.4 mg/kg) followed by bolus to a total dose of 30 mg | Acceleromyography (TOF-Watch SX*) | Sugammadex 100 mg (2 mg/kg); Pre reversal TOF ratio: 0.2; Post reversal TOF ratio: 1.0 (2 min) | Uneventful extubation and recovery |
| Gurunathan & Duncan, 2015 | Australia | 60/M; 70 kg | Myotonic dystrophy | Laparoscopic cholecystectomy; 45 min | Propofol, midazolam, Remifentanil infusion | Rocuronium 50 mg | Qualitative neuromuscular | Sugammadex 200 mg (approx 3 mg/kg); Pre reversal TOF ratio: 0.9 (1.5 min) | Uneventful extubation and recovery |
| Author/year        | Country            | Patient characteristics | Disease                  | Type of surgery; Duration of surgery | Anesthetic agents                     | NMBA | NM monitoring                                                                 | Dose of sugammadex & results of NM monitor | Postoperative course                      |
|-------------------|--------------------|-------------------------|--------------------------|--------------------------------------|---------------------------------------|------|-----------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------|
| Kendigelen et al., 2015 | Turkey            | 52/M; 75 kg             | Dermatomyositis          | Ileostomy; 110 min                   | Propofol, remifentanil induction       | Rocuronium 0.6 mg/kg as bolus        | Acceleromyography (TOF-Watch SX®)          | Sugammadex 2 mg/kg (150 mg); Pre reversal TOF ratio: 0.40; Post reversal TOF ratio: 0.9 (1 min) | Uneventful extubation and recovery        |
| Kosinova et al., 2016 | Czech Republic     | 27/F; 90 kg; 39+4 weeks gestation | Becker’s myotonia congenita | Elective caesarean section; around 40 min | Propofol target controlled infusion, sufentanil | Rocuronium 1 mg/kg                    | Acceleromyography (TOF-Watch SX®)          | Sugammadex 4 mg/kg; Pre reversal TOF: 0; Post reversal TOF: 0.98 (2 min 15 s) | Uneventful extubation and recovery        |
| Creaney et al., 2018 | Ireland            | 25/F; 61 kg; 146 cm; BMI: 28.6 kg/m²; 30+6 weeks gestation | Congenital muscular dystrophy | Elective caesarean section; N.R | Intravenous dexmedetomidine slow bolus followed by maintenance infusion throughout the procedure; Propofol induction followed by maintenance of propofol target controlled infusion; humidified high flow nasal oxygen | Rocuronium 1 mg/kg | Qualitative neuromuscular monitoring | Sugammadex 12 mg/kg in total; Pre reversal TOF count: 0; Post reversal TOF count: 0.95 (5 min) | Transferred to intensive care unit with dexmedetomidine infusion and extubated to non-invasive ventilation later, with pre-pregnancy BiPAP settings achieved in 24 h |
| Teixeira et al., 2019 | Portugal           | 37/M; 65 kg; 173 cm      | Myotonic dystrophy type 1 (Steinert disease) | Laparoscopic cholecystectomy; 60 min | Propofol and remifentanil target-controlled infusion for induction and maintenance | Rocuronium 25 mg (0.04 mg/kg) | Acceleromyography | Sugammadex: 150 mg (appr 2.3 mg/kg); Pre reversal TOF count: 2; Post reversal TOF count: 4, ratio: 0.96 (< 5 min) | Uneventful extubation and recovery        |
| Mangla et al., 2019  | USA                | 46/F; 63 kg; 170 cm      | Myotonic dystrophy       | Robotic assisted laparoscopic total abdominal hysterectomy and bilateral salpingo-oophorectomy; 3 h | Propofol induction followed by maintenance with fentanyl bolus, propofol and remifentanil infusions | Rocuronium 30 mg (0.48 mg/kg) | Qualitative neuromuscular monitoring (orbicularis oculi muscle) | Sugammadex 240 mg (3.8 mg/kg); Pre reversal TOF count: 0 (only weak post-tetanic counts were present); Post reversal TOF count: 4 (not clearly stated) (10 min) | Uneventful extubation and recovery        |

**Notes:**
- TOF: Train of four
- PTC: Post tetanic count
- N.R: Not reported
- NMBA: Neuromuscular blocking agent
- NM: Neuromuscular
reported delayed neuromuscular recovery time of 10 min [43, 49], but no explanations were given. It is possible that slight underdosing of sugammadex could have contributed to the delay with Mangla et al. [49]. Three authors had used 1 mg/kg rocuronium to aid intubation, possibly related to their rapid sequence induction [50–52]. With all these cases, standard recommended doses of sugammadex were administered according to the TOF count and TOF ratio of 0.9 was reached within reasonable time (<3 min). While response times to both rocuronium and sugammadex were not delayed, Stourac et al. observed prolonged duration of paralysis with rocuronium [51].

Polymyositis and dermatomyositis cause symmetrical weakness of proximal muscles due to an inflammatory process of the muscle itself with no impact on neuromuscular junction. However, two case reports on the use of sugammadex in patients with dermatomyositis, describe a delay in complete neuromuscular blockade (up to around 5 min), which the authors attribute to vascular pathology associated with the disease process resulting in slow diffusion of rocuronium to neuromuscular junction [53, 54] (Table 3). Prolonged reversal time with sugammadex [54] was observed by Suzuki et al. while the other two reports concluded that reversal time was unaffected in these inflammatory myopathies.

Neuropathies (Table 4)
A number of neuromuscular disorders could be grouped under neuropathies. One report on transverse myelitis and one report on multiple sclerosis were selected for this review (Table 4). Multiple sclerosis is a frequently occurring demyelinating neuropathy. The reports on multiple sclerosis patients did not suggest an altered dose of rocuronium or unusual response to sugammadex. However, a resistance to rocuronium was described by Staikou et al. manifesting as delay in onset of action following 1 mg/kg of rocuronium [55]. Transverse myelitis involves myelin destruction due to spinal cord inflammation. Prolonged paralysis was reported in a patient with transverse myelitis following the administration of 1.2 mg/kg rocuronium for rapid sequence induction [56].

Motor neuron diseases (Table 5)
Motor neuron diseases are a group of disorders characterized by progressive motor neuron degeneration, the most common of which is amyotrophic lateral sclerosis (ALS). It mainly involves lower motor neurons although in ALS both upper and lower motor neurons are affected [57]. In a patient with ALS reported by Kelsaka et al., clinical signs of inadequate recovery were observed despite a TOF ratio >0.90. Two minutes after sugammadex 2 mg/kg was administered, the patient recovered clinically and was extubated uneventfully [58] (Table 5). A similar discrepancy between TOF ratio and clinical signs of muscle strength recovery was also reported by Chang et al. [59, 60]. These authors henceforth questioned the reliability of TOF ratio to guide extubation in patients with this condition and proposed that this discordance may be related to the site and the severity of disease [59–61]. In fact, in patients reversed with sugammadex, a TOF ratio of 0.9 may not guarantee complete reversal without complete recovery of first twitch height (T1) [62]. Interestingly, no such issue was noticed by Yoo et al. in their patients with ALS or progressive muscle atrophy (PMA) in spite of their preexisting bulbar dysfunction. However, they had administered 5 mg/kg sugammadex as the pre-reversal TOF count was zero [63].

Use of sugammadex has also been investigated in patients with other motor neuron diseases (Table 5). Patients with spinobulbar muscular atrophy (Kennedy’s disease) are at increased risk of laryngospasm and bulbar dysfunction and therefore aspiration [64]. Administration of sugammadex 2 mg/kg with TOF count of 1 has been reported to have resulted in 100% reversal within 180 s in a patient with Kennedy’s disease [65]. Two papers reported the management of patients with spinal muscular atrophy [13, 66]. Although an immediate and adequate response to sugammadex was observed in both these patients, an increased sensitivity and prolonged paralysis from rocuronium was reported by Vilela et al. [66].

Based on our literature search, the implications for the use of sugammadex can be found as endnotes.

Other relevant considerations of sugammadex
Use of sugammadex does not guarantee adequate recovery unless confirmed by TOF ratio of at least 0.96. Since sugammadex does not form complexes with suxamethonium and benzylisoquinolinium muscle relaxants (mivacurium, atracurium and cisatracurium), it cannot be used to reverse these agents [67]. Although an immediate and adequate response to sugammadex was observed in both these patients, an increased sensitivity and prolonged paralysis from rocuronium was reported by Vilela et al. [66].

5Discordance between TOF ratios and clinical recovery have been reported in amyotrophic lateral sclerosis, which has been stated to be related to severity of disease and type of muscles involved.
6Quantitative neuromuscular monitor is essential in the management of these patients with a TOF ratio of >0.9 at peripheral muscles before extubation, to ensure adequate pharyngeal function and airway protection as well as to prevent complications such as atelectasis and pneumonia.
7Since delayed or failed recurarisation and long recovery times have been reported with adequately dosed sugammadex reversal even in normal surgical patients, presence of additional factors such as renal dysfunction, temperature fluctuation, acid-base or electrolyte imbalances in these patients or interaction with other medications (i.e. magnesium, baclofen,) necessitate prolonged post-operative observation, especially for respiratory insufficiency in patients with neuromuscular diseases.
| Author/ year | Country | Patient characteristics | Disease Type | Type of surgery; Duration of surgery | Anesthetic agents | NMBA | NM monitoring | Dose of sugammadex & results of NM monitor | Postoperative course |
|-------------|---------|-------------------------|--------------|-------------------------------------|------------------|------|--------------|------------------------------------------|---------------------|
| Weekes et al., 2010 | Ireland | 38/F; 70 kg | Idiopathic transverse myelitis | Elective cesarean section; 60 min | Thiopentone and rapid sequence induction followed by maintenance with morphine, sevoflurane/oxygen/nitrous oxide; propofol infusion during delayed extubation | Rocuronium 1.2 mg/kg | Qualitative neuromuscular monitoring | Initial neostigmine 5 mg (0.07 mg/kg) & glycopyrollate 1 mg; Pre reversal TOF: four weak TOF twitches; Post reversal TOF: 4 weak twitches (for more than 1 h); Sugammadex 4 mg/kg administered (delayed administration because of unavailability) followed by all the clinical signs of adequate recovery in 2 min | Uneventful extubation and recovery |
| Staikou and Rekatsina, 2017 | Greece | 31/F; 62 kg; 164 cm; BMI: 23.1 kg/m² | Multiple sclerosis | Myectomy; 65 min | Benzodiazepine premedication. Propofol, fentanyl induction followed by maintenance with fentanyl boluses, sevoflurane, nitrous oxide/oxygen | Rocuronium 1 mg/kg for intubation with no further doses | Neuromuscular module of S/5 anaesthesia monitor | Sugammadex 2 mg/kg; Pre reversal TOF count: 3; Post reversal TOF ratio: 0.9 (0.75 min) | Uneventful extubation and recovery. |

TOF: Train of four; PTC: Post tetanic count; N.R: Not reported; NMBA: Neuromuscular blocking agent; NM: Neuromuscular

*Using facial nerve*
| Author/year | Country | Patient characteristics | Disease | Type of surgery; Duration of surgery | Anesthetic agents | NMBA | NM monitoring | Dose of sugammadex & results of NM monitor | Postoperative course |
|-------------|---------|-------------------------|---------|-------------------------------------|------------------|------|--------------|-----------------------------------------|---------------------|
| Vilela et al., 2012 | Portugal | 61/M; 85 kg; 175 cm; BMI: 278 kg/m² | Spinal muscular atrophy | Elective percutaneous atrial septal defect (ostium secundum) closure; 117 min | Propofol, remifentanil induction followed by maintenance with propofol, remifentanil infusion | Rocuronium 40 mg (0.47 mg/kg) | Acceleromyography (TOF-Watch SX®) | Sugammadex 170 mg (2 mg/kg); Pre reversal TOF ratio: 0.62, Post reversal TOF ratio: 0.90 (69 s) | Uneventful extubation and recovery |
| Franco-Hernández et al., 2013 | Spain | 2 siblings; Case 1: 47/F; 162 cm; BMI: 23.4 kg/m² | Spinal muscular atrophy | Elective cholecystectomy; N.R. Case 2: Laparoscopic subtotal colectomy and ileostomy; N.R. | Propofol, midazolam, Fentanyl induction (both) followed by maintenance with sevoflurane, remifentanil infusion (Case 1) propofol and remifentanil infusion (Case 2) | Rocuronium 0.6 mg/kg; no further boluses | Qualitative neuromuscular monitoring | Sugammadex 2 mg/kg; Pre reversal: moderate neuromuscular blockade; Post reversal TOF ratio: > 0.9 | Uneventful extubation and recovery in both cases |
| Kelsaka et al., 2013 | Turkey | 47/M; 70 kg | Amyotrophic lateral sclerosis (Lou Gehrig’s disease) | Fracture neck of humerus; 75 min | Propofol, remifentanil induction followed by maintenance with remifentanil infusion, sevoflurane/oxygen/air | Rocuronium 40 mg (0.29 mg/kg) | Acceleromyography (TOF-Watch SX®) | Sugammadex 160 mg (4 mg/kg); Pre reversal TOF: 0.9 (2.8 min) | Uneventful extubation and recovery |
| Stewart et al., 2013 | Australia | 61/F; 40 kg; 162 cm; BMI: 152 kg/m² | Spinal muscular atrophy | Combined approach tympanoplasty; 118 min | Propofol, remifentanil induction followed by maintenance with propofol and remifentanil, oxygen / air | Rocuronium 40 mg (0.57 mg/kg) | Acceleromyography (TOF-Watch SX®) | Sugammadex 150 mg (2 mg/kg); Pre reversal TOF: 0.9 (2.8 min) | Uneventful extubation and recovery |
| Takeuchi, R et al., 2014 | Japan | 62/M; 70 kg; 173 cm; BMI: 234 kg/m² | Kennedy’s disease (Spinal bulbar muscular atrophy) | Frontal sinusectomy; N.R. | Propofol, remifentanil induction followed by maintenance with propofol and remifentanil infuson, oxygen / air and fentanyl bolus end of surgery | Rocuronium 40 mg (0.57 mg/kg) | Quality neuromuscular monitoring | Sugammadex 100 mg (1 mg/kg); Pre reversal TOF: 0.9 (2.8 min) | Extubation 5 min after sugammadex; Uneventful recovery |
| Chang et al., 2014 | Korea | 47/M; 38 kg; 165 cm; BMI: 14 kg/m² | Amyotrophic lateral sclerosis | Total thyroidectomy with cervical node dissection; anaesthesia time 405 min | Propofol, remifentanil target-controlled infusion for induction and maintenance oxygen / air and fentanyl bolus end of surgery | Rocuronium 0.3 mg/kg for intubation; Additional 10 mg bolus during the procedure | Acceleromyography (TOF-Watch SX®) | Sugammadex 1 mg/kg; Pre reversal TOF: 0.98, but with inadequate tidal volume and difficulty in opening eyes; Post reversal TOF not stated; but increase in depth of breathing and able to open eyes spontaneously after 2 min. | Uneventful extubation and recovery |
| Chang et al., 2017 | Korea | 62/F; 52 kg; 167 cm; BMI: 186 kg/m² | Amyotrophic lateral sclerosis | Ureteroscopic ureterolithotomy; 84 min | Propofol induction followed by maintenance with sevoflurane, oxygen/air. No details on opioids | Rocuronium 20 mg bolus (0.38 mg/kg) | Acceleromyography (TOF-Watch SX®) | Sugammadex 100 mg (192 mg/kg); Pre reversal TOF: 0.65; Post reversal TOF: > 0.90 (80 s). In spite of TOF > 0.9, additional 100 mg (1.92 mg/kg) sugammadex administered due to reduced postoperative transfer to ICU and ventilated for 4 hours followed by uneventful extubation and recovery | Postoperative extubation and recovery for 4 days |
| Author/year | Country | Patient characteristics | Disease | Type of surgery; Duration of surgery | Anesthetic agents | NMBA | NM monitoring | Dose of sugammadex & results of NM monitor | Postoperative course |
|-------------|---------|-------------------------|---------|--------------------------------------|------------------|------|--------------|--------------------------------------------|-------------------|
| Yoo et al., 2017 | Korea | Case 1: 54/M; 70 kg; 175 cm; BMI: 23 kg/m² | Case 1: Progressive muscular atrophy Case 2: Amyotrophic lateral sclerosis | Case 1: Removal of intramedullary nail left femur and plate left humerus; 160 min Case 2: Split thickness skin grafting lower limb; 60 min | Case 1 & 2: Premedication with glycopyrrolate. Propofol with lignocaine induction, continuous remifentanil infusion; maintenance with desflurane and fentanyl bolus at the end of surgery. | | | Case 1: Sugammadex 200 mg (2.86 mg/kg). Pre-reversal TOF: 0.15 Post-reversal TOF 1.25 (3 min) | Uneventful extubation and recovery |
| | | Case 2: 66/F; 40 kg; 154 cm; BMI: 17 kg/m² | | | | | | Case 2: Sugammadex 200 mg (5 mg/kg). Pre-reversal TOF: 0 Post-reversal TOF 1.15 (4 min) | |
| Tada et al., 2019 | Japan | 54/F; 48 kg; 156 cm; BMI: 19.7 kg/m² | Hereditary spastic paraplegia | Decompressive laminectomy; Duration of surgery: N.R. | Propofol, remifentanil for induction followed by maintenance with fentanyl boluses and remifentanil infusion with desflurane/oxygen/air | Rocuronium 20 mg for intubation followed by 20 mg rocuronium as boluses to a total of 40 mg | TOF -Watch (NIHON KOHDEN Corporation, Japan) | Sugammadex 100 mg (2 mg/kg); Pre-reversal TOF: N.R. Post-reversal TOF count: 4 (ratio > 0.9) | Uneventful extubation and recovery |

* Two cases reported in this paper are given under two different sections.

TOF: Train of four; PTC: Post tetanic count; N.R: Not reported; NMBA: Neuromuscular blocking agent; NM: Neuromuscular.
fact, even in routine surgical population, in spite of reversing with sugammadex, 2% of the patients were found to have residual paralysis (TOF < 0.9) in the recovery room [70]7. Fluctuations in muscle power may occur even after seemingly adequate reversal with sugammadex due to the redistribution of unbound muscle relaxant from the peripheral to the central compartment causing a rebound of blockade [71]. Despite the rapid reversal, there is no firm evidence to prove superiority of sugammadex over neostigmine in the prevention of postoperative pulmonary complications according to a recent review [72].

There have been reports of suspected hypersensitivity reactions to sugammadex [73, 74] but more evidence is needed in this regard to confirm its true incidence. In addition, there are concerns about displacement and capturing interactions with sugammadex. In particular, sugammadex may capture the prostagentic compound in oral contraceptive making it less effective [10]. Sugammadex is not also recommended for patients with severe renal impairment or those on dialysis [75] although evidence suggests that the complex with rocuronium can be removed by haemodialysis [76].

Limitations of the review
There are several limitations to this review. As this review summarizes the findings of various case reports, there are inherent drawbacks as missing information, inability to draw inferences on causality and publication bias [77]. Non-English reports, abstracts without full texts and pediatric case reports are not included in this review. Since the primary goal of this article is to investigate the use of sugammadex patients in neuromuscular disorders and its clinical considerations, details on the disease severity and medications in every reported case were avoided. Since based on case reports, it has not been possible to provide conclusive evidence on the correct dose and timing of administration of sugammadex in patients with neuromuscular disorders.

Conclusion
Anesthetic management of patients with neuromuscular disorders is challenging due to the variability in the type, severity of the disorder and the extent of dysfunction in various muscle groups and their sensitivity to muscle relaxants in each patient. Multiple case reports have been published describing the successful reversal of rocuronium with sugammadex in patients with neuromuscular disorders, however, there are also reports of adverse reactions and instances of inadequate reversal with administration of sugammadex. Currently, as there is limited knowledge on optimal dosing and timing of administration of sugammadex, a similar unpredictability in response also seem to occur with the use of sugammadex in this cohort of patients. Hence despite the advantages of sugammadex in this high-risk group of patients, it is strongly recommended to use quantitative neuromuscular monitoring to ensure complete recovery from the effects of steroidal muscle relaxants and to exercise extended postoperative supervision in these patients.

Abbreviations
ALS: Amyotrophic lateral sclerosis; APM: Adductor pollicis; CSM: Corrugator supercilii; MeSH: Medical Subject Headings; PM: Progressive muscular atrophy; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; T1: First twitch

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Authors' contributions
UG conceived this study. UG and LS performed the initial literature search of the databases. UG and SK screened the title and abstracts of all the articles from the literature search to select articles as well as extracted the data. LS was the third reviewer to resolve any disagreements between UG and SK. LS performed manual search of the reference list of the selected articles for additional articles. All the authors were involved in drafting the manuscript and approved the final version.

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