



Mapping the current evidence on the anesthetic management of adult patients with neuromuscular disorders—a scoping review

Cartographie des données probantes actuelles sur la prise en charge anesthésique des patients adultes atteints de maladies neuromusculaires : une étude de portée

Luuk R. van den Bersselaar, MD · Madelief Gubbels, BSc · Sheila Riazi, MD ·
Luc Heytens, MD, PhD · Heinz Jungbluth, MD, PhD · Nicol C. Voermans, MD, PhD ·
Marc M. J. Snoeck, MD, PhD

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Abstract

Purpose Patients with neuromuscular disorders (NMDs) are at increased risk of perioperative complications. The objective of this scoping review was to examine emerging evidence from published studies, case reports, and review articles on anesthetic management of patients with NMDs, following the methodological frame for scoping reviews.

Sources We searched PubMed and EMBASE for articles published between 1 January 2000 and 14 July 2021.

Principal findings Three prospective and 21 retrospective studies on altered pharmacokinetics and

pharmacodynamics of neuromuscular blocking agents (NMBA) in NMD patients were included. Furthermore, 168 case reports/series reporting 212 anesthetics in 197 patients were included. These studies showed that preanesthetic neuromuscular monitoring can be used for precise NMBA dosing in myasthenia gravis patients. Sugammadex was associated with fewer postoperative myasthenic crises. Perioperative complications were not associated with specific anesthetic agents. Case reports/series showed that in 32% (67/212) of anesthetics, at least one complication was reported. Unexpected intensive care unit admission was a frequently reported complication. Patients with a complicated disease course may have had a higher use of succinylcholine (unadjusted relative risk,

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L. R. van den Bersselaar, MD (✉)
Department of Anaesthesiology, Malignant Hyperthermia
Investigation Unit, Canisius Wilhelmina Hospital, Nijmegen,
The Netherlands
e-mail: luuk.vandenbersselaar@radboudumc.nl

Department of Neurology, Cognition and Behaviour, Donders
Institute for Brain, Radboud University Medical Center,
Nijmegen, The Netherlands

M. Gubbels, BSc · N. C. Voermans, MD, PhD
Department of Neurology, Cognition and Behaviour, Donders
Institute for Brain, Radboud University Medical Center,
Nijmegen, The Netherlands

S. Riazi, MD
Department of Anaesthesiology and Pain Medicine, Malignant
Hyperthermia Investigation Unit, University Health Network,
University of Toronto, Toronto, ON, Canada

L. Heytens, MD, PhD
Malignant Hyperthermia Research Unit, University of Antwerp,
Antwerp, Belgium

H. Jungbluth, MD, PhD
Department of Paediatric Neurology, Neuromuscular Service,
Evelina's Children Hospital, Guy's and St Thomas' Hospitals
NHS Foundation Trust, London, UK

Department of Basic and Clinical Neuroscience, IoPPN, King's
College, London, UK

Randall Division for Cell and Molecular Biophysics, Muscle
Signalling Section, King's College, London, UK

M. M. J. Snoeck, MD, PhD
Department of Anaesthesiology, Malignant Hyperthermia
Investigation Unit, Canisius Wilhelmina Hospital, Nijmegen,
The Netherlands

0.13; 95% confidence interval [CI], 0.20 to 0.86) and volatile anesthetics (adjusted odds ratio [OR], 0.38; 95% CI, 0.20 to 0.73; $P = 0.004$).

Conclusion Evidence on the anesthetic management and perioperative complications of patients with NMDs is mainly based on small retrospective studies and case reports. Further clinical trials or large retrospective studies are required to investigate the choice of safe anesthetic agents. Main areas of interest are the potential benefits of neuromuscular monitoring and sugammadex and the risks possibly associated with volatile anesthetics and succinylcholine.

Résumé

Objectif Les patients atteints de maladies neuromusculaires (MNM) courent un risque accru de développer des complications périopératoires. L'objectif de cette étude de portée est de résumer les connaissances émergentes tirées des études, présentations de cas et comptes rendus publiés portant sur l'anesthésie des patients atteints de MNM, tout en suivant le cadre méthodologique d'une étude de portée.

Constatations principales ont été incluses trois études prospectives et 21 études rétrospectives comprenant des patients atteints de MNM chez lesquels les myorelaxants ont eu des propriétés pharmacocinétiques et pharmacodynamiques modifiées. En outre, 168 présentations / séries de cas portant sur 212 gestes d'anesthésie chez 197 patients ont été incluses. Ces études ont démontré qu'un suivi neuromusculaire peut être utilisé en pré-anesthésie pour ajuster les doses de myorelaxant chez les patients atteints de myasthénie grave. En postopératoire, un taux plus faible de crises de myasthénie grave a été observé avec le sugammadex. Aucune relation entre les anesthésiques et les complications périopératoires n'a été détectée. Dans les présentations / séries de cas, les patients ayant eu au moins une complication représentaient 67 (32 %) des cas. L'admission non programmée en réanimation est une complication fréquemment rapportée. Les patients dont la maladie s'est dégradée plus rapidement ont possiblement reçu des doses plus fortes de succinylcholine (risque relatif non ajusté 0,13, intervalle de confiance [IC] 95 %, 0,20 à 0,86) et d'agents volatils (rapport de cotes [RC] ajusté, 0,38 (IC 95 %, 0,20 à 0,73), $P = 0.004$).

Sources Les articles sont issus des bases de données PubMed et EMBASE (articles publiés entre le 1^{er} janvier 2000 et le 14 juillet 2021).

Conclusion Les données probantes sur la prise en charge anesthésique et les complications périopératoires affectant les patients atteints de MNM sont principalement fondées sur de petites études rétrospectives et des cas cliniques. Des études cliniques ou rétrospectives d'envergure sont

nécessaires pour orienter le choix de la technique d'anesthésie optimale. Les principaux domaines d'intérêt sont les bienfaits potentiels du monitoring neuromusculaire et de l'utilisation de sugammadex ainsi que les effets indésirables possibles des anesthésiques volatils et de la succinylcholine.

Keywords anesthesia · malignant hyperthermia · myopathy · neuromuscular disorders · perioperative adverse events

Perioperative care of patients with neuromuscular disorders (NMDs) is challenging. Although not uncommon as a group, most NMDs are rare and the experience with specific conditions can be limited among anesthesiologists.¹ NMDs are highly diverse clinically and genetically, with over 500 different diagnoses and an even wider range of disease manifestations and comorbidities.² Despite the differences between specific disorders, anesthetic risks and considerations have a significant overlap, as, for example, neuromuscular transmission defects or cardiorespiratory involvement are common to many NMDs and have important implications for perioperative care.^{3–6} Other major concerns are the association of some NMDs with impaired thermoregulation due to a reduced muscle mass, malignant hyperthermia (MH), and anesthesia-induced rhabdomyolysis (AIR).⁷ In addition, side effects of frequently used anesthetic agents are more pronounced in neuromuscular patients because of upregulation of $\alpha 7$ nicotinic acetylcholine and possibly endorphin receptors.^{8–11}

Because most NMDs are rare, there are only few prospective clinical studies concerning the anesthetic management of these patients. Current knowledge regarding this topic is based on retrospective studies, small case series, case reports, consensus statements, and expert opinion-based reviews.^{11–13} We recently organized the 259th European Neuromuscular Centre (ENMC) international workshop on anesthesia and NMDs. The main aims of the workshop were to work on a consensus statement among international experts on the anesthetic management of patients with NMDs and to explore future international collaborative research possibilities.¹⁴ The major goal of this scoping review was to examine and to summarize the nature and extent of the current evidence on the anesthetic management of patients with motor neuron diseases, poly(radiculo)neuropathies, neuromuscular junction disorders, and muscle disorders including acquired and inherited myopathies, muscular dystrophies, and (non)dystrophic myotonias. Another goal of this

scoping review was to focus on the nature and extent of perioperative complications in patients with NMDs and the association of volatile anesthetics, neuromuscular monitoring, neuromuscular blocking agents (NMBAs), and antagonists with well-known complications in NMD patients such as MH, AIR, residual muscle relaxation, and pulmonary complications. This scoping review also evaluated knowledge gaps that can guide future research and may contribute to the education of relevant healthcare professionals.

Methods

This review was conducted using the methodological framework for scoping reviews as reported by Levac *et al.*¹⁵ and is reported according to the PRISMA extension reporting guideline for scoping reviews.¹⁶ Methods of the search strategy, inclusion and exclusion criteria, and data analysis were specified and documented in advance.

Stage 1: Identifying the research question

Our study population comprised adult patients with an NMD, who needed sedation or anesthesia for an operation or a nonsurgical intervention. Neuromuscular disorders included motor neuron diseases, poly(radiculo)neuropathies, neuromuscular junction disorders, and muscle disorders including acquired and inherited myopathies, muscular dystrophies, and (non)dystrophic myotonias. This study population represented a broad spectrum of NMDs, with one general research question: what is the current evidence on the anesthetic management of patients with an NMD?

Stage 2: Identifying relevant studies

We searched PubMed and EMBASE for clinical studies, retrospective studies, case series/reports, and systematic/narrative reviews on the anesthetic management of patients with NMDs.

We searched the following databases on 14 July 2021:

- PubMed, The United States National Library of Medicine at the National Institutes of Health, from 1 January 2000.
- EMBASE, Elsevier, from 1 January 2000.

The search was developed in collaboration with the information specialist from the medical library at the Radboud University in consultation with the authors. We used a broad search strategy, comprising three main categories: neuromuscular disorders, anesthesia, and perioperative complications. For each main category,

relevant Medical Subject Headings terms, keywords, and synonyms were combined using “OR” within the categories. These three separate main categories were combined using “AND.” No limitation, except for the date, was applied. We did not search other databases or gray literature.

Details of the search strategy can be found in the Electronic Supplementary Material (ESM), eAppendix 1.

Stage 3: Study selection

Eligibility assessment was performed by two authors (L. B. and M. G.) in a blinded and standardized manner using a two-step model. For the first step, all studies were reviewed for eligibility based on title and abstract. In case of discrepancy between the reviewing authors, consensus was reached by discussion. When no consensus was reached, a third author (N. V.) was asked to make the final decision.

We included articles on anesthetic management of NMDs from four different levels of evidence criteria:

- Prospective clinical studies on the anesthetic management of patients with an NMD.
- Retrospective studies on the effect of anesthetic management of patients with an NMD.
- Case reports or case series reporting the anesthetic management and perioperative outcome of patients with an NMD with need for anesthesia or procedural sedation for surgery or invasive diagnostic procedures.
- Review articles or consensus statements on the anesthetic management of patients with an NMD. Although it is uncommon to include review articles, the level of evidence on this topic is extraordinarily low and sometimes even fully based on expert opinion. We are aware that the level of evidence of these review articles is low, but believe that a summary of expert opinion in the field of anesthesia and NMDs might help map current evidence and guide future research.

Articles matching the following criteria were excluded:

- Studies reporting perioperative risks or complications with a focus on surgical techniques/complications.
- Studies reporting patients with NMD predominantly located above the motor neuron (e.g., primary lateral sclerosis).
- Studies reporting pediatric cases (age < 18 yr) because anesthetic management, indication for surgery, and the neuromuscular diagnosis of these patients differ significantly from adult patients with NMD and would have resulted in having a very heterogeneous group.
- Responses to published articles.
- Nonclinical studies (e.g., laboratory studies).

- Animal studies.

For the second step, we reviewed the full texts of the studies considered eligible to make a final decision about inclusion. After exploring the available literature, inclusion and exclusion criteria for the second step were tightened for the review articles and clinical studies as outlined in detail below.

All case reports and case series reporting the anesthetic management and outcome of patients with NMDs matching the inclusion criteria were included. Since most literature focused on the association of perioperative complications in patients with an NMD with AIR, MH, and pharmacological strategies, we included studies and reviews if least one of the following topics was studied:

- The perioperative complications of specific NMDs or NMDs in general.
- The association of MH or AIR with specific NMDs.
- The use of NMBAs and their antagonists in specific NMDs or NMDs in general.
- The perioperative use of cholinesterase inhibitors in patients with myasthenia gravis (MG) in relation to perioperative complications.

During the second step of study selection, the following articles were excluded:

- Reviews published before 2015 since these articles are mainly based on literature published between 2000 and 2015. Inclusion of review articles published before 2015 might have led to recommendations based on outdated literature.
- Review articles written by one author since these articles lack a multidisciplinary approach.
- Articles in any language other than English.

Stage 4: Charting the data

We developed a separate data extraction sheet for clinical/retrospective studies, case studies, and review articles. The data extraction sheets were pilot tested on five randomly selected clinical/retrospective studies, case studies, and review articles and subsequently refined accordingly. Data were extracted independently by two authors (L. B. and M. G.).¹⁷ For each study, we extracted the perioperative complication rate of patients with a specific NMD or NMDs in general, and the use of cholinesterase inhibitors (in patients with MG), NMBAs, volatile anesthetics, and sugammadex in the study population.

For each case study, we extracted the age, sex, publication date, neuromuscular diagnosis (including information if the diagnosis was known before surgery), type of surgery (including emergency or elective),

anesthesia technique, anesthetic agents used, administration of NMBAs and their antagonists, whether neuromuscular monitoring was used, and the perioperative disease course (complicated or uncomplicated). In the patients with MG, we registered the perioperative use of cholinesterase inhibitors. In the patients with a complicated disease course, we registered the specific complications. All perioperative complications were registered, without distinction between complications, that were very likely caused by the anesthesia or by a more uncertain etiology. A case was classified as complicated when an adverse event or unexpected condition of a patient occurred during or following a medical action resulting in irreversible damage and/or need for medical treatment.

For each review article, we extracted which NMDs were associated with MH or AIR when exposed to volatile anesthetics and/or succinylcholine, and which NMBAs and antagonists appear to be safe in patients with a specific NMD, or NMDs in general.

Stage 5: Synthesis of results

Case reports and case series were assessed for perioperative complications. In case of more than one anesthetic in the same patient, available data from all anesthetics were used for the statistical analysis. The anesthetic agents/NMBAs used, the type of surgery, anesthetic technique, and the use of neuromuscular monitoring were presented as numbers and percentages for the whole study population, and separately for the patients with a complicated and uncomplicated perioperative disease course, respectively. Additionally, the difference between those characteristics in the patients with a complicated and uncomplicated disease course were analyzed as categorical data using logistic regression with these characteristics as the independent variable, publication year as covariate, and a complicated/uncomplicated disease course as the dependent variable. We used the publication year as covariate since anesthetic practice varied during the study period (e.g., sugammadex was introduced during the study period, and neuromuscular monitoring became stricter and commonly used). We considered *P* values of < 0.05 significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

Since there are no high-quality methodologies for an objective quality assessment of narrative reviews, selection based on quality of the review articles would lead to a significant selection bias. Therefore, we did not perform a quality assessment, and information regarding the authors' opinion on the topics described in stage 3 is presented as categorical data without triage.

Results

We identified 4,525 articles matching our search strategy. After removal of duplicates and screening titles and abstracts, 490 articles were considered relevant (Cohen's κ coefficient, 0.78). Subsequently, we reviewed the full-texts and included 219 articles for data extraction (Cohen's κ coefficient, 0.89). The study selection process and reasons for exclusion are summarized in the [Figure](#). Details on the included articles can be found in [ESM eAppendix 2](#).

Clinical studies

We did not identify any prospective clinical studies on the effect of anesthetic interventions on perioperative complications in patients with NMDs. The only three prospective clinical studies identified investigated the pharmacodynamics of nondepolarizing NMBAs in NMD patients. These studies showed that the train-of-four (TOF) ratio before administration of an NMBA is a good predictor for atracurium and rocuronium requirement in patients with MG.^{18,19} Another pharmacodynamic study showed that, in patients with oculopharyngeal muscular dystrophy (OPMD), the onset time of cisatracurium was prolonged while the duration of action was normal compared with healthy controls.²⁰

Retrospective studies

We identified 21 retrospective studies matching our inclusion criteria of which eight studied described perioperative complications in MG patients undergoing thymectomy.^{21–28} Patients with MG had more preoperative complications and a higher frequency of reintubation following thymectomy than non-MG patients did.²¹ Postoperative myasthenic crisis (POMC) occurred in 0–18.2% of patients^{22,25–27} and was shown to be associated with a history of a previous myasthenic crisis and unstable MG.²² Prolonged mechanical ventilation varied between 4.5–13.1% (> 24 hr)^{23,25} and 3.7% (> 48 hr).²¹ Apart from the study of Mouri *et al.*,²⁶ which reported less POMC when sugammadex was used, perioperative complications could not be associated with specific anesthetic agents/management.

Other studies were on the anesthetic management of patients with myotonic dystrophy type I (DMI)^{29,30} and II,^{31,32} amyotrophic lateral sclerosis,^{33–35} Duchenne muscular dystrophy,³⁶ glycogen storage disease,³⁷ inclusion body myositis,³⁸ Lambert–Eaton myasthenic syndrome,³⁹ mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes mitochondrial encephalomyopathy⁴⁰ and OPMD.⁴¹ Opioid use was

possibly associated with postoperative complications in a small retrospective study on the anesthetic management of DMI.³⁰ In this group of “other studies” the complication rates varied from 0% to 54%. Respiratory complications were frequently reported. Because sample sizes were small, lack of any complications or a control cohort perioperative complication could not be associated with specific anesthetic agents/management. Results of the retrospective studies included are summarized in [Table 1](#).

Case reports

We included 168 case reports or case series reporting a total of 212 anesthetics in 197 different patients. There was a slight female predominance in the reported cases (117/212; 55%). Median [interquartile range] age was 41 [27–57] yr. Myasthenia gravis was a frequent neuromuscular diagnosis (67/212; 32%), followed by DMI (38/212; 18%) and McArdle's disease (22/212; 10%). The neuromuscular diagnosis was known before surgery in 176/194 (91%) cases. The neuromuscular diagnosis may have been more frequently known before surgery in the uncomplicated group than in the complicated group (adjusted odds ratio [OR], 18.6; 95% confidence interval [CI], 4.06 to 85.0; $P < 0.001$). Nevertheless, this analysis lacks validity because of the small proportion of patients in which the neuromuscular diagnosis was unknown before surgery in the group of patients with an uncomplicated disease course (unadjusted relative risk, 6.4; 95% CI, 1.7 to 23.9). Gastrointestinal surgery (46/212; 22%), gynecological surgery (35/212; 17%), and thymectomy (29/212; 14%) were frequent indications for surgery. In 155/187 (83%) cases, surgery was elective. Surgery may have been more frequently elective in the uncomplicated group than in the complicated group (adjusted OR, 2.34; 95% CI, 1.07 to 5.1; $P = 0.03$). Demographics and details regarding the neuromuscular diagnosis and type of surgery are summarized in [Table 2](#).

In 145/212 (68%) of the reported cases, surgery, anesthesia, and perioperative course of disease were uncomplicated. At least one complication was reported in 67/212 (32%) cases. Death was reported in 5/212 (2%) patients. Unexpected postoperative intensive care unit (ICU) admission (19/212; 9%), unplanned postoperative reintubations (18/212; 9%), and unplanned postoperative need for mechanical ventilation (17/212; 8%) were frequently reported complications. All reported complications and their frequencies are summarized in [Table 3](#).

Succinylcholine may have been more frequently used in patients with a complicated disease course (adjusted OR, 0.05; 95% CI, 0.01 to 0.39; $P = 0.004$). Nevertheless, this analysis lacks validity because of the small proportion of

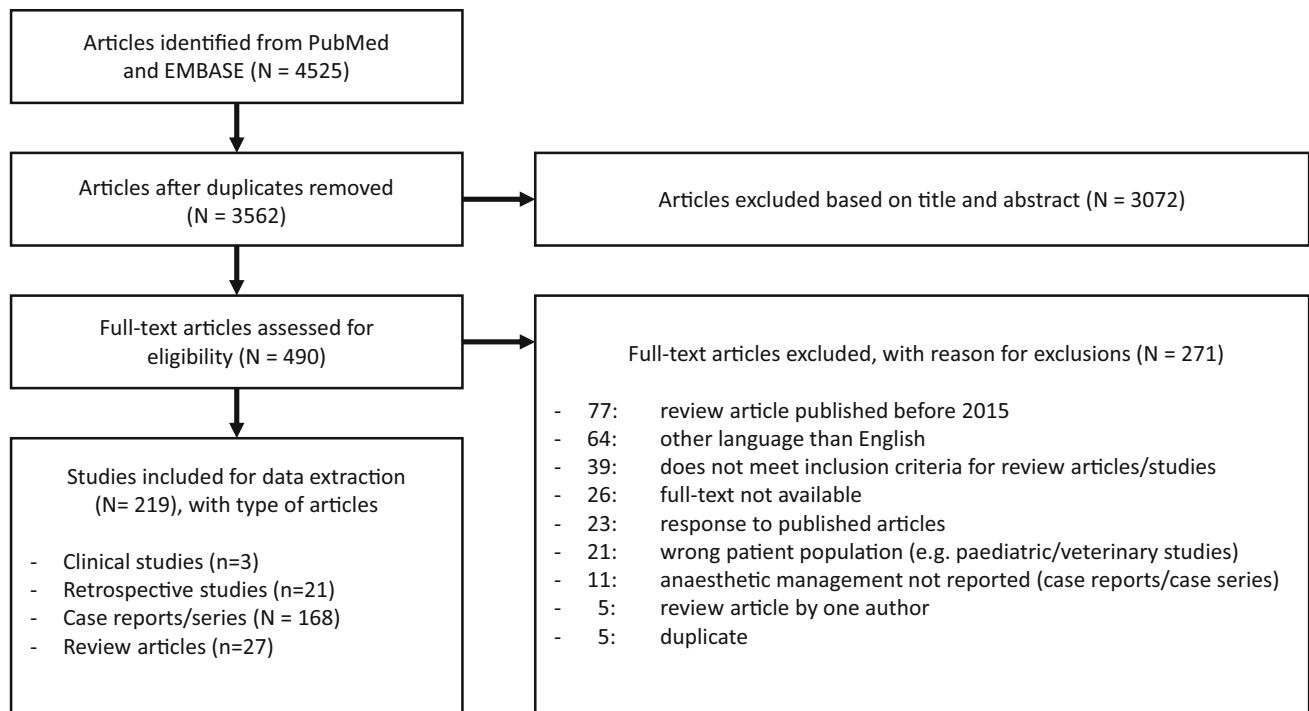


Figure Summary of the study selection process

patients in which the neuromuscular diagnosis was unknown before surgery in the group of patients with an uncomplicated course of disease (unadjusted relative risk, 0.13; 95% CI, 0.20 to 0.86). Volatile anesthetics may have been more frequently used in patients with a complicated disease course (adjusted OR, 0.38; 95% CI, 0.20 to 0.73; $P = 0.004$). Based on the available data from all included cases, there was no significant difference in the use of NMBAs (adjusted OR, 0.62; 95% CI, 0.31 to 1.24; $P = 0.17$) and the use of neuromuscular monitoring between the patients with a complicated (adjusted OR, 1.90, 95% CI, 0.82 to 4.43; $P = 0.14$) and uncomplicated course of disease. There was no significant difference in the use of NMBA antagonists between patients with an uncomplicated and complicated disease course (adjusted OR, 0.58; 95% CI, 0.25 to 1.36; $P = 0.21$). Sugammadex was associated with an uncomplicated perioperative disease course in univariate analysis (OR, 3.40; 95% CI, 1.25 to 9.3; $P = 0.02$). Based on the available data from all included cases, there was no significant difference effect after adding publication year as a covariate (adjusted OR, 2.57; 95% CI, 0.86 to 7.7; $P = 0.09$). Propofol infusion syndrome was not reported. Details regarding the anesthetic technique, use of NMBAs, NMBA antagonists, and neuromuscular monitoring can be found in Table 4.

Review articles

We included 27 review articles matching our inclusion criteria. Four focused solely on MH-related NMDs. The others discussed the anesthetic management of several specific NMDs or NMDs in general, and some included a section about MH-related NMDs.

There is consensus concerning the risk of succinylcholine in patients with an NMD. The authors of all except one review article stated that the use of succinylcholine should be avoided. In addition, all authors except one stated that nondepolarizing NMBA are safe in NMD patients as long as they are used with caution (i.e., dose reduction and/or with neuromuscular monitoring). All authors except one stated that sugammadex is safe for patients with NMDs. The use of volatile anesthetics in NMD patients remains a matter of debate among the authors of the included reviews. Recommendations regarding the safe use of anesthetic agents based on the reviews included are summarized in Table 5.

Several review articles considered central core disease (CCD), King-Denborough syndrome (KDS), multi-minicore disease (MmD), and Native American myopathy as MH-related NMDs.^{7,11,13,42,61–63}

Table 1 Retrospective/observational studies on perioperative complications in patients with neuromuscular disorders

| Neuromuscular disorder (intervention) | Number of GAs | Complication rate | Most reported complication | NMBA | SUG | VOL | CEI continued (in case of MG) |
|---|---------------|----------------------------|-----------------------------|------|-------|------|-------------------------------|
| Myasthenia gravis (thymectomy) | | | | | | | |
| Alshaikh <i>et al.</i> ²¹ | 108 | 7–3%* | Reintubation | NR | NR | NR | NR |
| Ando <i>et al.</i> ²² | 55 | ≥ 18% | POMC | 0% | NA | NR | 53% |
| Fujita <i>et al.</i> ²³ | 66 | 5% | MV > 24hr | 9% | 0% | 99% | 91% |
| Kas <i>et al.</i> ²⁴ | 324 | 22–54%** | Reintubation | NR | NR | NR | 0%*** |
| Lu <i>et al.</i> ²⁵ | 61 | 23% | Prolonged MV | NR | NR | NR | 0%*** |
| Mouri <i>et al.</i> ²⁶ | 795 | ≥ 22–≥ 25%*** (OR 0.48) | POMC | NR | 63.6% | NR | 13 - 21% |
| Saylan <i>et al.</i> ²⁷ | 15 | 0% | NA | 100% | 100% | NR | 100% |
| Vymazal <i>et al.</i> ²⁸ | 117 | 0% | NA | 100% | 100% | 100% | NR |
| Myotonic dystrophy I (general) | | | | | | | |
| Imison ²⁹ | 18 | 6% | Atelectasis | 39% | 0% | ≥6% | NA |
| Kim <i>et al.</i> ³⁰ | 51 | 22% | Respiratory | NR | NR | NR | NA |
| Myotonic dystrophy II (general) | | | | | | | |
| Kirzinger <i>et al.</i> ³¹ | 340 | 0.6–20%** | PONV | NR | NR | NR | NA |
| Weingarten <i>et al.</i> ³² | 39 | 0% | NA | 82% | NR | 57% | NA |
| Amyotrophic lateral sclerosis (general) | | | | | | | |
| Hoepfer <i>et al.</i> ³³ | 18 | 22% | Prolonged hospitalization | 17% | NR | 100% | NA |
| Amyotrophic lateral sclerosis (diaphragm pacemaker placement) | | | | | | | |
| Onders <i>et al.</i> ³⁴ | 51 | 0% | NA | 0% | NA | 100% | NA |
| Amyotrophic lateral sclerosis (PEG) | | | | | | | |
| Liu <i>et al.</i> ³⁵ | 9 | 0% | NA | 0% | NA | 0% | NA |
| Duchenne muscular dystrophy (PEG) | | | | | | | |
| Boivin <i>et al.</i> ³⁶ | 8 | 13% | Difficult airway | NR | NR | NR | NA |
| Glycogen storage disease (general) | | | | | | | |
| Gurrieri <i>et al.</i> ³⁷ | 28 | 0% | NA | 68% | NR | NR | NA |
| Inclusion body myositis (general) | | | | | | | |
| Mortenson <i>et al.</i> ³⁸ | 18 | 0% | NA | 78% | NR | 61% | NA |
| Lambert–Eaton myasthenic syndrome (general) | | | | | | | |
| Weingarten <i>et al.</i> ³⁹ | 46 | 11% | Respiratory | 50% | NR | 83% | NR |
| MELAS (general) | | | | | | | |
| Gurrieri <i>et al.</i> ⁴⁰ | 20 | 10% | Acute renal failure | 90% | NR | 70% | NA |
| Ocular pharyngeal muscular dystrophy (levator palpebrae resection/cricopharyngeal myotomy) | | | | | | | |
| Pellerin <i>et al.</i> ⁴¹ | 92 | 25% | Severe coughing and choking | 96% | NR | NR | NA |

*The authors made a distinction between narrow and broad composite complications

**The authors made a distinction between major and minor complications

***Cholinesterase inhibitors were temporally suspended

CEI = cholinesterase inhibitor, GA = general anesthesia, MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, MG = myasthenia gravis, MV = mechanical ventilation, NA = not applicable, NMBA = neuromuscular blocking agent, NR = not reported, PEG = percutaneous endoscopic gastrostomy, POMC = postoperative myasthenic crisis, PONV = postoperative nausea and vomiting, SUG = sugammadex, VOL = volatile anesthetics

Table 2 Patient demographics, neuromuscular diagnoses, and surgical details

| Characteristic | Uncomplicated disease course <i>N</i> = 145 | Complicated disease course <i>N</i> = 67 | Total <i>N</i> = 212 | Unadjusted odds ratio (95% CI), <i>P</i> value | Adjusted odds ratio (95% CI), <i>P</i> value |
|---|--|---|-------------------------|---|---|
| Sex | | | | | |
| Male | 60/145 (41%) | 35/67 (52%) | 95/212 (45%) | 0.65 (0.36 to 1.16), 0.14 | 0.60 (0.33 to 1.10), 0.09 |
| Female | 85/145 (59%) | 32/67 (48%) | 117/212 (55%) | | |
| Age (yr) | | | | | |
| Median [IQR] | 42 [28–57] | 39 [22–58] | 41 [27–57] | <i>P</i> = 0.15 | - |
| Neuromuscular diagnosis | | | | | |
| Myasthenia gravis | 40/145 (28%) | 27/67 (40%) | 67/212 (32%) | | |
| Myotonic dystrophy type I | 29/145 (20%) | 9/67 (13%) | 38/212 (18%) | - | - |
| McArdle's disease | 20/145 (14%) | 2/67 (3%) | 22/212 (10%) | | |
| Amyotrophic lateral sclerosis | 9/145 (6%) | 4/67 (6%) | 13/212 (6%) | | |
| Becker muscular dystrophy | 4/145 (3%) | 3/67 (5%) | 7/212 (3%) | | |
| Kearns–Sayre syndrome | 6/145 (4%) | 0/67 (0%) | 6/212 (3%) | | |
| Duchenne muscular dystrophy | 5/145 (3%) | 0/67 (0%) | 5/212 (2%) | | |
| Other mitochondrial myopathies | 4/145 (3%) | 1/67 (2%) | 5/212 (2%) | | |
| Central core disease | 3/145 (2%) | 1/67 (2%) | 4/212 (2%) | | |
| Limb-girdle muscular dystrophy | 3/145 (2%) | 1/67 (2%) | 4/212 (2%) | | |
| MELAS | 3/145 (2%) | 1/67 (2%) | 4/212 (2%) | | |
| Other* | 19/145 (13%) | 18/67 (27%) | 37/212 (18%) | | |
| Neuromuscular diagnosis known before surgery | | | | | |
| Yes | 126/145 (98%) | 50/67 (76%) | 176/194 (91%) | 20.2 [#] (4.47 to 90.9), <0.001 | 18.6 [#] (4.06 to 85.0), <0.001 |
| No | 2/145 (2%) | 16/67 (24%) | 18/194 (9%) | | |
| Not reported ** | - | - | 18 | | |
| Elective or emergency surgery | | | | | |
| Elective | 106/145 (88%) | 49/67 (74%) | 155/187 (83%) | 2.45 (1.13 to 5.3), 0.02 | 2.34 (1.07 to 5.1), 0.03 |
| Emergency | 15/145 (12%) | 17/67 (26%) | 32/187(17%) | | |
| Not reported ** | - | - | 25 | | |
| Type of surgery | | | | | |
| Gastrointestinal | 33/145 (23%) | 13/67 (19%) | 46/212 (22%) | | |
| Gynecology | 23/145 (16%) | 12/67 (18%) | 35/212 (17%) | - | - |
| Thymectomy | 14/145 (10%) | 15/67 (22%) | 29/212 (14%) | | |
| Cardiac | 19/145 (13%) | 4/67 (6%) | 23/212 (11%) | | |
| Orthopedic | 13/145 (9%) | 5/67 (7%) | 18/212 (9%) | | |
| Ear-nose-throat/neck | 12/145 (8%) | 6/67 (9%) | 18/212 (9%) | | |
| Orthognathic/dental | 3/145 (2%) | 6/67 (9%) | 9/212 (4%) | | |
| Plastic/reconstructive | 5/145 (3%) | 1/67 (1%) | 6/212 (3%) | | |
| Urology | 2/145 (1%) | 3/67 (4%) | 5/212 (2%) | | |
| Breast | 4/145 (3%) | 0/67 (0%) | 4/212 (2%) | | |
| Cardiac + thymectomy | 4/145 (3%) | 0/67 (0%) | 4/212 (2%) | | |
| Other* | 13/145 (9%) | 2/67 (3%) | 15/212 (7%) | | |

All numbers are *n*/group *N* (%) unless otherwise specified. The two columns on the right report results of unadjusted and adjusted analyses of the association with a complicated disease course of sex, whether or not the neuromuscular diagnosis was known before surgery, and elective vs emergency surgery.

*Sum of all categories with ≤ 3 reported anesthetics per category; **excluded from the statistical analysis

[#] Odds ratios are correctly calculated but are invalid because of the small proportion of patients in which the neuromuscular diagnosis was not known before surgery in the group of patients with an uncomplicated course of disease. Unadjusted relative risk = 6.4 (95% CI, 1.7 to 23.9)

CI = confidence interval; IQR = interquartile range; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

Table 3 Reported perioperative complications

| | <i>N</i> = 212 |
|--|------------------|
| Uncomplicated | 145/212 (68%) |
| Respiratory | |
| Postoperative unplanned reintubation | 18/212 (9%) |
| Unplanned need for postoperative mechanical ventilation | 17/212 (8%) |
| Hypoxemia | 8/212 (4%) |
| Pneumonia | 5/212 (2%) |
| Difficult airway | 4/212 (2%) |
| Atelectasis | 3/212 (1%) |
| Tracheostomy placement during postoperative ICU admission | 2/212 (0.9%) |
| Postoperative need for noninvasive mechanical ventilation | 2/212 (0.9%) |
| Failure to wean from ventilator during postoperative ICU admission | 1/212 (0.5%) |
| Bronchospasm | 1/212 (0.5%) |
| Hemodynamic | |
| Cardiac arrhythmias | 5/212 (2%) |
| Hypotensive episode | 5/212 (2%) |
| Cardiopulmonary resuscitation | 4/212 (2%) |
| Decompensated heart failure | 3/212 (1%) |
| Myocardial infarction | 1/212 (0.5%) |
| Neurologic/neuromuscular | |
| Residual muscle relaxation* | 10/212 (5%) |
| Postoperative progression of muscle weakness | 8/212 (4%) |
| Myasthenic crisis | 5/212 (2%) |
| Delayed postoperative arousal from anesthesia | 4/212 (2%) |
| Masseter spasm | 2/212 (0.9%) |
| Seizures | 2/212 (0.9%) |
| Rhabdomyolysis | 2/212 (0.9%) |
| Generalized myotonia | 1/212 (0.5%) |
| Malignant hyperthermia reaction | 1/212 (0.5%) |
| Other | |
| Unexpected postoperative ICU admission | 19/212 (9%) |
| Death | 5/212 (2%) |
| Surgical complication | 4/212 (2%) |
| Acute kidney failure with need for hemodialysis | 2/212 (0.9%) |
| Metabolic | 1/212 (0.5%) |

All numbers are *n*/group *N* (%) unless otherwise specified

*Residual muscle relaxation was defined as inefficient respiratory effort post extubation due to residual muscle relaxation and/or the unexpected need for postoperative sedation and ICU admission for mechanical ventilation due to residual muscle relaxation

ICU = intensive care unit

Centronuclear myopathy^{62,63} and periodic paralysis^{7,62} were both considered as MH-related NMDs by two reviews articles and possibly MH associated by one review article.^{7,64} Association with MH susceptibility was not assumed in any of the review articles on Emery–Dreifuss muscular dystrophy,⁵¹ DMI^{52,53}, and mitochondrial myopathies.^{11,60} Reviews were less unanimous about the MH risk of other NMDs. The association of MH with several NMDs according to the included reviews is summarized in Table 6.

Discussion

This scoping review provides an overview of the nature and extent of published clinical studies, retrospective studies, case reports, and review articles concerning anesthesia and NMDs, focusing on the clinical data. Literature on this topic consists of studies with low levels of evidence such as case reports/case series, review articles, and a few small retrospective studies. The main findings of this scoping review and their interpretation are discussed below.

Use of neuromuscular blocking agents and antagonists

Although the level of evidence identified in this scoping review was considerably low, we were able to identify some evidence on the use of NMBAs and its antagonists in patients with NMDs.

First, succinylcholine may have been associated with a complicated perioperative course of disease in the reported cases (unadjusted relative risk, 0.13; 95% CI, 0.20 to 0.86), and there was consensus among all but one of the authors of the review articles. We did not identify any clinical studies or retrospective studies on this topic. Therefore, the true severity and prevalence of life-threatening side effects such as hyperkalemia, rhabdomyolysis, and myotonia remain uncertain. Due to the association of severe side effects of succinylcholine in patients with NMDs and the availability of alternative NMBAs, prospective clinical studies on this topic are probably not feasible and future research on this topic will be limited to retrospective studies. Until more evidence on the risks of succinylcholine becomes available, the use of succinylcholine should probably be avoided when feasible.

Second, the use of NMBAs was not associated with perioperative complications in the case reports included in this scoping review (adjusted OR, 0.62; 95% CI, 0.31 to 1.24, *P* = 0.17). Apart from one, all authors of the review articles considered the use of nondepolarizing NMBAs as safe, or safe as long as they are used with caution (e.g., after dose reduction and/or when using concomitant

Table 4 Anesthetic technique, neuromuscular blocking agent use, neuromuscular blocking agent antagonist use, and neuromuscular monitoring

| Characteristic | Uncomplicated disease course <i>N</i> = 145 | Complicated disease course <i>N</i> = 67 | Total <i>N</i> = 212 | Unadjusted odds ratio (95% CI), <i>P</i> value | Adjusted odds ratio (95% CI), <i>P</i> value |
|--|--|---|-------------------------|---|---|
| Anesthetic technique | | | | | |
| General anesthesia | 102 (70%) | 52 (78%) | 154 (73%) | - | - |
| Spinal anesthesia | 11 (8%) | 3 (5%) | 14 (7%) | | |
| General + epidural anesthesia | 6 (4%) | 5 (8%) | 11 (5%) | | |
| Epidural anesthesia | 10 (7%) | 1 (2%) | 11 (5%) | | |
| Combined spinal epidural anesthesia | 4 (3%) | 1 (2%) | 5 (2%) | | |
| Other* | 12 (9%) | 5 (7%) | 17 (8%) | | |
| Neuromuscular blocking agent | | | | | |
| Yes | 64/108 (59%) | 40/59 (68%) | 104 (62%) | 0.69 (0.35 to 1.35), | 0.62 (0.31 to 1.24), |
| No | 44/108 (41%) | 19/59 (32%) | 63 (38%) | 0.28 | 0.17 |
| Not applicable** | - | - | 45 | | |
| Succinylcholine | | | | | |
| Yes | 1/108 (1%) | 10/59 (17%) | 11 (7%) | 0.05 [#] (0.01 to 0.37), | 0.05 [#] (0.01 to 0.39), |
| No | 107/108 (99%) | 49/59 (83%) | 156 (93%) | 0.004 | 0.004 |
| Not applicable** | - | - | 45 | | |
| Volatile anesthetics | | | | | |
| Yes | 40/108 (37%) | 36/59 (61%) | 76 (46%) | 0.38 (0.20 to 0.72), | 0.38 (0.20 to 0.73), |
| No | 68/108 (63%) | 23/59 (39%) | 91 (55%) | 0.003 | 0.004 |
| Not applicable* | - | - | 45 | | |
| Neuromuscular monitoring | | | | | |
| Yes | 43/64 (67%) | 22/40 (55%) | 65 (63%) | 1.68 (0.74 to 3.78), | 1.90 (0.82 to 4.43), |
| No | 21/64 (33%) | 18/40 (45%) | 39 (38%) | 0.21 | 0.14 |
| Not applicable** | - | - | 108 | | |
| Neuromuscular blocking agent antagonists used (not specified) | | | | | |
| Yes | 32/64 (50%) | 23/40 (58%) | 55 (53%) | 0.74 (0.33 to 1.64), | 0.58 (0.25 to 1.36), |
| No | 32/64 (50%) | 17/40 (43%) | 49 (47%) | 0.46 | 0.21 |
| Not applicable** | - | - | 108 | | |
| Sugammadex used | | | | | |
| Yes | 24/64 (37%) | 6/40 (15%) | 30 (29%) | 3.40 (1.25 to 9.3), | 2.57 (0.86 to 7.7), |
| Yes | 40/64 (63%) | 34/40 (85%) | 74 (71%) | 0.02 | 0.09 |
| No | - | - | 108 | | |
| Not applicable** | | | | | |
| Continuation of cholinesterase inhibitors in myasthenia gravis patients | | | | | |
| Yes | 25/33 (76%) | 15/24 (62%) | 40 (70%) | 2.14 (0.66 to 7.0), 0.20 | 1.88 (0.59 to 6.0), |
| No | 8/33 (24%) | 9/24 (38%) | 17 (30%) | | 0.28 |

Table 4 continued

| Characteristic | Uncomplicated disease course/ <i>N</i> = 145 | Complicated disease course/ <i>N</i> = 67 | Total <i>N</i> = 212 | Unadjusted odds ratio (95% CI), <i>P</i> value | Adjusted odds ratio (95% CI), <i>P</i> value |
|-------------------|--|---|----------------------|--|--|
| Not reported*** | - | - | 10 | | |
| Not applicable*** | - | - | 145 | | |

All numbers are *n*/group *N* (%) unless otherwise specified. The two columns on the right report results of unadjusted and adjusted analyses of the association with a complicated perioperative disease course of the use of neuromuscular blocking agents, succinylcholine, volatile anesthetics, neuromuscular monitoring, neuromuscular blocking agent antagonists, sugammadex, and continuation of cholinesterase inhibitors in myasthenia gravis patients.

*Sum of all categories with ≤ 3 reported anesthetics per category

**Only patients with general anesthesia (with or without additional epidural or plexus anesthesia) were included in the statistical analysis

*** Only cases in which neuromuscular blocking agents were used were included in the statistical analysis

****Only patients with myasthenia gravis in which cholinesterase inhibitors use was reported were included in the statistical analysis

Odds ratios are correctly calculated but are invalid because of the small proportion of patients in which succinylcholine was used in the group of patients with an uncomplicated course of disease. Unadjusted relative risk, 0.13; 95% CI, 0.20 to 0.86

CI = confidence interval

neuromuscular monitoring). The presence of a complicated disease course was not associated with the use of neuromuscular monitoring in the case reports included in this scoping review. Nevertheless, the sample size was probably insufficient to answer this research question as reflected in the remarkably wide confidence interval (OR, 1.90; 95% CI, 0.82 to 4.43).

Except for pharmacokinetic and pharmacodynamic studies, we did not identify any clinical studies or retrospective studies on the effect of nondepolarizing NMBAs or neuromuscular monitoring on perioperative disease course in patients with NMDs.²⁰ Future research should focus on pharmacokinetic and pharmacodynamic studies on different nondepolarizing NMBAs and NMDs to give more insights into whether and how pharmacodynamics and pharmacokinetics are altered for each specific NMBA and/or NMD. This might help guide personalized dose adjustments in patients with specific NMDs. Furthermore, the effect of nondepolarizing NMBAs and neuromuscular monitoring on perioperative disease course in patients with NMDs might be interesting areas for future studies. Especially considering the results from studies in the healthy population.⁶⁵ Until these studies have been conducted, nondepolarizing NMBAs can probably be used with caution (use of neuromuscular monitoring and dose adjustments in individual cases). Although reliable evidence in favor of using of neuromuscular monitoring in patients with NMDs is missing, neuromuscular monitoring is harmless and has been shown to be associated with less postoperative residual paralysis in the general population.⁶⁵ If available, use of neuromuscular monitoring is therefore recommended whenever muscle relaxation is required by NMBAs in NMD patients.

Third, the use of sugammadex was associated with less POMC after thymectomy in a large cohort of MG patients.²⁶ Other studies did not show beneficial effect of sugammadex in patients with NMDs. But due to the small sample size and lack of a control cohort or sometimes even lack of any complication, the methodology and power of these studies was insufficient to answer this research question. Furthermore, sugammadex was only introduced a few years ago in the USA and Canada. Therefore, large and well-performed clinical studies in this specific subgroup of patients are not yet available. In the case reports included in this scoping review, there was no statistically significant difference in the use of sugammadex between NMD patients with a complicated versus uncomplicated disease course. Nevertheless, its use has only been reported in 30 case reports, which is an inadequate sample size to draw conclusions as reflected in the wide confidence interval (adjusted OR, 2.57; 95% CI, 0.86 to 7.7; *P* = 0.09).

We identified two cases of incomplete reversal of rocuronium-induced neuromuscular blockade with sugammadex in MG patients.^{66,67} In both cases, the TOF ratio was restored sufficiently after administration of neostigmine. Exacerbation of MG symptoms, sometimes leading to a myasthenic crisis, occurs frequently after transsternal thymectomy.²⁴ Worsening of myasthenia status with increase in muscle weakness might be caused by the interruption of immunosuppressive agents, perioperative sepsis, surgical stress, pregnancy, or interference from anesthetic drugs (volatile anesthetics or opioids). Acetylcholinesterase inhibitors are an effective treatment for MG, and complete recovery of the TOF ratio by neostigmine administration after prior use of sugammadex may therefore be explained by its

Table 5 Included review article authors' recommendations regarding the use of succinylcholine, nondepolarizing neuromuscular blocking agents, sugammadex, and volatile anesthetics in patients with NMDs

| Anesthetic agent | Is safe | Can be used with caution* | Should be avoided |
|---|------------------|---------------------------|-------------------|
| Use of succinylcholine | | | |
| Neuromuscular disorders in general | - | - | (11–13,42,43) |
| Myasthenia gravis | - | (12) | (13,44–48) |
| Metabolic/mitochondrial myopathy | - | - | (13,49,50) |
| Amyotrophic lateral sclerosis | - | - | (44) |
| Dystrophies in general | - | - | (13,44,51) |
| Myotonic dystrophy type I | - | - | (13,52,53) |
| Myotonic dystrophy type II | - | - | (53) |
| Limb-girdle muscular dystrophy | - | - | (13,54) |
| Duchenne muscular dystrophy | - | - | (12,13,55) |
| Becker muscular dystrophy | - | - | (12,13,55,56) |
| Merosin-deficient congenital dystrophy | - | - | (57) |
| Lambert–Eaton myasthenic syndrome | - | (12) | - |
| King-Denborough Syndrome | - | - | (13) |
| Central core disease | - | - | (13) |
| Multi-minicore disease | - | - | (13) |
| Centronuclear myopathy | - | - | (13) |
| Congenital fiber type disproportion | - | - | (13) |
| Nemaline myopathy | - | - | (13) |
| Periodic paralysis | - | - | (13) |
| Nondystrophic myotonias | - | - | (13) |
| Collagen VI-related myopathy | - | - | (58) |
| Use of nondepolarizing neuromuscular blocking agents | | | |
| Neuromuscular disorders in general | (59) | (11,13,43,47) | - |
| Myasthenia gravis | (44) | (12,13,47,48) | (46) |
| Metabolic/mitochondrial myopathy | (49) | (13,50,60) | - |
| Dystrophies in general | (55) | (13,44,51) | - |
| Myotonic dystrophy type I | - | (13,52,53) | - |
| Myotonic dystrophy type II | - | (53) | - |
| Limb-girdle muscular dystrophy | - | (13,54) | - |
| Duchenne dystrophy | (55) | (12,13) | - |
| Becker dystrophy | (56) | (12,13) | - |
| Merosin-deficient congenital dystrophy | - | (57) | - |
| Lambert–Eaton myasthenic syndrome | - | (12) | - |
| King-Denborough syndrome | - | (13) | - |
| Central core disease | - | (13) | - |
| Multi-minicore disease | - | (13) | - |
| King-Denborough syndrome | - | (13) | - |
| Centronuclear myopathy | - | (13) | - |
| Congenital fiber type disproportion | - | (13) | - |
| Nemaline myopathy | - | (13) | - |
| Periodic paralysis | (13) | - | - |
| Nondystrophic myotonias | (13) | - | - |
| Collagen VI-related myopathy | - | - | (58) |
| Use of sugammadex | | | |
| Neuromuscular disorders in general | (11,59) | - | - |
| Myasthenia gravis | (12,13,45,46,48) | - | - |
| Dystrophies in general | (13) | (51) | - |

Table 5 continued

| Anesthetic agent | Is safe | Can be used with caution* | Should be avoided |
|--|---------------|---------------------------|-------------------|
| Myotonic dystrophy type I | (13,52,53) | - | - |
| Myotonic dystrophy type II | (53) | - | - |
| Limb-girdle muscular dystrophy | (13,54) | - | - |
| Duchenne dystrophy | (12,13) | - | - |
| Becker's dystrophy | (12,13,56) | - | - |
| Volatile anesthetics | | | |
| Neuromuscular disorders in general | - | (13) | (11) |
| Myasthenia gravis | (12,13,44–48) | - | - |
| Lambert–Eaton | (12) | - | - |
| Metabolic/mitochondrial myopathy | (11,13,49,50) | (60) | - |
| Dystrophies in general | - | (13) | (44,51) |
| Myotonic dystrophy type I | (11,53) | (13,52) | - |
| Myotonic dystrophy type II | (53) | - | - |
| Limb-girdle muscular dystrophy | - | (13) | (54) |
| Duchenne dystrophy | - | (13) | (11,12,55) |
| Becker dystrophy | - | (13) | (12,55) |
| Merosin-deficient congenital dystrophy | - | - | (57) |
| King-Denborough syndrome | - | - | (13) |
| Central core disease | - | - | (13) |
| Multi-minicore disease | - | - | (13) |
| King-Denborough syndrome | - | - | (13) |
| Centronuclear myopathy | - | - | (13) |
| Congenital fiber type disproportion | - | - | (13) |
| Nemaline myopathy | - | - | (13) |
| Periodic paralysis | - | - | (13) |
| Collagen VI related myopathy | - | - | (58) |

Numbers are reference numbers (cf. References). Only NMDs discussed in the included reviews are presented. Information regarding the authors' opinion is presented as categorical data without triage.

*Authors recommended using these agents only if the dose is adjusted and the effect is measured using a neuromuscular monitor

NMD = neuromuscular disorders

anticholinergic effect rather than by its reversal of the neuromuscular blockade by rocuronium.

Apart from one large retrospective study in MG patients,²⁶ there is currently insufficient evidence on the risks and benefits of sugammadex in NMD patients. Future pharmacokinetic and pharmacodynamic studies could offer clarification of cases of incomplete reversal of muscle relaxations as discussed above. Given the beneficial effect of sugammadex on pulmonary complications in the general population,⁶⁸ this might be an interesting area for future prospective clinical studies and/or retrospective studies. Until these studies have been conducted, the effect of sugammadex on reversal of neuromuscular blockade should be appropriately monitored with TOF ratio

recovery and specific attention to the 100% twitch recovery before extubation.

Volatile anesthetics

The use of volatile anesthetics in patients with NMDs remains a matter of debate. There are no prospective or retrospective studies on this topic. Analysis of the case reports included in this scoping review indicated that use of volatile anesthetics may be associated with a complicated perioperative disease course (adjusted OR, 0.38; 95% CI, 0.20 to 0.73; $P = 0.004$).

Several authors have expressed concerns regarding the AIR risk in patients with NMDs in general and in muscular dystrophy patients in particular.^{11–13,44,51,54,55}

Table 6 The association of neuromuscular disorders with malignant hyperthermia susceptibility based on the present scoping review

| Neuromuscular diagnosis* (genes associated with this NMD) | MH-related NMD | Possibly MH-related NMD | Uncertain | NMD not related with MH |
|--|--------------------|-------------------------|-----------|-------------------------|
| Central core disease (<i>RYRI</i>) | (7,11,13,42,61–63) | - | - | - |
| King-Denborough syndrome (<i>RYRI</i>) | (7,11,13,42,61–63) | - | - | - |
| Multi-minicore disease (<i>RYRI</i>) | (7,11,13,42,62,63) | - | - | - |
| Native American myopathy (<i>STAC3</i>) | (7,13,42) | - | - | - |
| Centronuclear myopathy (<i>X-linked</i> , <i>MTM1</i> , <i>DNM2</i> , <i>BINI</i> , <i>RYRI</i>) | (62,63) | (7) | - | - |
| Nemaline myopathy (<i>ACTA1</i> , <i>NEB</i> , <i>RYRI</i>) | (11) | (7) | - | - |
| Evans myopathy (<i>RYRI</i>) | (11) | - | - | - |
| Brody disease (<i>ATP2A1</i>) | - | (61) | - | - |
| McArdle's (<i>PYGM</i>) | - | (61) | - | - |
| Periodic paralysis (<i>CACNAIS</i> and <i>SCN4A</i>) | (7,62) | (64) | - | - |
| Congenital fiber disproportion (<i>ACTA1</i> , <i>RYRI</i>) | (62) | (7) | - | - |
| Noonan syndrome (<i>PTPN11</i> , <i>KRAS</i> , <i>SOS1</i>) | - | (61) | - | - |
| Phosphoglucomutase deficiency type 1 (<i>PGM1</i>) | - | (61) | - | - |
| Dystrophies in general | (44) | - | - | (11,51) |
| Limb-girdle muscular dystrophy | - | (54) | - | - |
| Duchenne muscular dystrophy (X) | (43) | - | - | (55) |
| Becker muscular dystrophy (X) | - | (56) | - | (55) |
| Emery–Dreifus muscular dystrophy (<i>EMD</i> , <i>LMNA</i>) | - | - | - | (51) |
| Merosin-deficient congenital dystrophy (<i>LAMA-2</i>) | - | - | (57) | - |
| Myotonic dystrophy type I (<i>DMPK</i>) | - | - | - | (52,53) |
| Mitochondrial myopathies | - | - | - | (11,60) |
| Benign samaritan congenital myopathy (<i>RYRI</i>) | (62) | - | - | - |
| Collagen VI-related myopathy (<i>COL6A1</i> , <i>COL6A2</i> , <i>COL6A3</i>) | - | - | - | (58) |

Numbers are reference numbers (cf. References).

* Only NMDs discussed in the included reviews are presented. Genes associated with MH are printed in bold.

MH = malignant hyperthermia, NMD = neuromuscular disorder

Nevertheless, although AIR is a well-known perioperative complication in patients with muscular dystrophies, a causal relationship of AIR with volatile anesthetics has never been unequivocally proven. We identified only one report of an 18-year-old obese patient with Becker muscular dystrophy who suffered a hyperkalemic cardiac arrest and rhabdomyolysis after the use of isoflurane for a six-hour procedure.⁶⁹ To test for susceptibility to MH, an *in vitro* caffeine halothane contracture test (IVCT) was performed three months later that turned out to be positive. In the absence of clear symptoms of hypermetabolism and ***RYRI/CACNAIS/STAC3*** variants, AIR might be a better diagnostic description indicating potential harmfulness of long-term exposure of volatile anesthetics. The IVCT has high false-positive rates in dystrophic patients.⁷⁰

Since we identified a very limited number of AIR cases, the risk of AIR in adult patients with NMDs seems low (Table 3). This rare occurrence within our cohort is

probably due to the pediatric age group being excluded, where muscular dystrophy and AIR are frequently described. In spite of the low number of AIR cases, the use of volatile anesthetics was possibly associated with a complicated disease course rather than by AIR. There are several explanations for this finding. In animal studies, sevoflurane has been shown to reduce the contraction force of the diaphragm.^{71,72} In addition, volatile anesthetics enhance the effect of nondepolarizing NMBAs, as illustrated by a prolonged duration of rocuronium action if coadministered with sevoflurane.^{73–75} This may lead to residual relaxation and reduced muscle force in NMD patients. Future studies or setting up a registry of all NMD patients exposed to volatile anesthetics might help to create an unbiased cohort and examine the prevalence and severity of AIR, residual paralysis, and pulmonary complications in NMD patients exposed to volatile anesthetics.

Although associated with serious complications and risks, volatile anesthetics do have desirable pharmacokinetic properties. Since evidence on this topic is limited, the risks and benefits of volatile anesthetics in patients with NMDs should be weighed on a case-by-case basis, taking into account the extent and duration of the surgery, the degree of muscle weakness (which may be enhanced by NMBAs), and/or disease-specific considerations such as the association with AIR and MH susceptibility of some NMDs. Neuromuscular monitoring should probably be used whenever NMBAs are used in combination with volatile anesthetics.

Propofol and propofol infusion syndrome

Although patients with mitochondrial myopathies are at increased risk of propofol infusion syndrome, we did not identify any studies or case reports in the body of literature we examined. Propofol infusion syndrome occurs mainly when patients are exposed to propofol for > 48 hr in the ICU.^{76,77} Propofol seems safe when used for procedural sedation and/or general anesthesia lasting for shorter time periods, even if those last up to several hours. In addition to our observation, there is international consensus concerning the safety of propofol in patients with mitochondrial disorders.⁷⁸ The choice between intravenous and volatile anesthesia must be made on a case-by-case basis. Based on current available evidence, we cannot recommend completely avoiding the use of either one in patients with NMDs.

Susceptibility to malignant hyperthermia

We did not identify any clinical/retrospective studies on this topic, possibly because of the low prevalence of NMDs and MH, excluding laboratory and pediatric studies and ethical limitations of prospective studies on this topic. There is consensus regarding the association of MH with *RYR1*-related myopathies (CCD, KDS, and MmD). Nevertheless, there are concerns about a potential relation with MH in a large number of NMDs without consensus among authors in the field of NMDs and anesthesiology (Table 6). The association of MH and some NMDs has been proven through direct genetic evidence in patients with NMDs due to mutations in *RYR1*,^{79,80} and, less frequently, in *CACNA1S*^{81–83} and *STAC3*.^{84,85} Patients with an NMD associated with variants in these genes might therefore be at risk for MH when exposed to triggering agents and should be referred to an MH unit to counsel and test for MH susceptibility.

There is currently no evidence for an association of other NMDs with MH. The association of some muscular dystrophies with MH made by some authors of the

included review articles is probably based on misdiagnosed cases of AIR.⁸⁶ Of course, patients with any Mendelian NMD may have an additional *RYR1/CACNA1S/STAC3* variant resulting in MH susceptibility. Nevertheless, this risk is similar to the low MH risk in the general population.

Limitations

Our scoping review has a number of limitations. First, the level of evidence we identified was very low. There is a lack of prospective studies on the relationship between anesthetic management and perioperative complications in patients with NMDs. Such studies are difficult to conduct because of the low prevalence of most NMDs. Many retrospective studies had a small sample size, high bias risk, and insufficient methodology to study specific effects of perioperative anesthetic management on disease course. Furthermore, due to the explorative nature of our study design and the small number of case reports, we were not able to draw reliable conclusions as reflected in the remarkable ORs and wide confidence intervals. For the same reasons, we were not able to perform multivariate analysis and/or meaningful subgroup analysis for specific NMDs. While patients with different NMDs have different complications, anesthetic management should be adapted accordingly. We were not able to compare complication type, complication rate, or anesthetic management with data from a control cohort. Additionally, the cohort included in the case report/case series section is a very selective patient population since more highly complex cases with significant and clinically relevant perioperative risks are published. Finally, it was not possible to perform an objective quality assessment of the review articles, and although all reviews had been peer-reviewed before publication, quality and evidence for the statements made were variable.

Conclusion

Patients with NMDs are at increased perioperative risk due to potential cardiorespiratory involvement and more pronounced side-effects of anesthetics and NMBAs. Current evidence on this topic is mainly based on small retrospective studies, case reports, and expert opinion-based reviews. To summarize all available evidence and knowledge on this topic, the participants of the 259th ENMC international workshop on anesthesia and neuromuscular disorders will work on consensus statements on anesthesia and NMDs, genetic counseling regarding the risk of MH susceptibility in patients with

RYR1-related myopathies, and a literature review on anesthesia and NMDs in pediatric patients.

Further clinical trials or large observational studies are required to investigate which anesthetic agents can be used safely and which should be avoided. Main areas of interest are the potential benefits of using neuromuscular monitoring and sugammadex and the risks possibly associated with volatile anesthetics and succinylcholine in patients with NMDs. Until these studies have been conducted, the use of succinylcholine should probably be avoided when feasible. Nondepolarizing NMBAs and sugammadex can probably be used safely with proper monitoring and dose adjustment. The use of volatile anesthetics should be guided by the extent and duration of the surgery and anesthesia, the degree of muscle weakness, and disease-specific considerations.

Author contributions Luuk R. van den Bersselaar contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. Madelief Gubbels contributed to the conception and design of the study; acquisition, and interpretation of data; and drafting the article. Sheila Riazi contributed to conception of the study, interpretation of data, and drafting the article. Luc Heytens contributed to the interpretation of data and drafting the article. Heinz Jungbluth contributed to conception of the study, interpretation of data, and drafting the article. Nicol C. Voermans contributed to the conception and design of the study, interpretation of data, and drafting the article. Marc M. J. Snoeck contributed to the conception and design of the study, interpretation of data, and drafting the article.

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