

Malignant Hyperthermia and Muscular Dystrophies

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BACKGROUND: Patients with muscular dystrophy have been reported to experience a variety of life-threatening complications during and after general anesthesia. We performed a systematic analysis to define the spectrum of anesthetic-related complications in patients with muscular dystrophy, with an emphasis on malignant hyperthermia susceptibility.

METHODS: A literature search was undertaken using multiple search engines and the appropriate articles were reviewed by the authors to determine anesthetic-associated complications in patients with muscular dystrophy. Of all the types of muscular dystrophy, Duchenne muscular dystrophy (DMD) and Becker dystrophy (BD) represent nearly all the anesthesia-related reports.

RESULTS: Anesthetic complications in patients with DMD and BD include intraoperative heart failure, inhaled anesthetic-related rhabdomyolysis (absence of succinylcholine), and succinylcholine-induced rhabdomyolysis and hyperkalemia.

CONCLUSION: We did not find an increased risk of malignant hyperthermia susceptibility in patients with DMD or BD compared with the general population. However, dystrophic patients who are exposed to inhaled anesthetics may develop disease-related cardiac complications, or rarely, a malignant hyperthermia-like syndrome characterized by rhabdomyolysis. This latter complication may also occur postoperatively. Succinylcholine administration is associated with life-threatening hyperkalemia and should be avoided in patients with DMD and BD.

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Malignant hyperthermia (MH) is an uncommon pharmacogenetic condition that results in a hypermetabolic cascade initiated at the skeletal muscle cell on exposure to volatile anesthetics and depolarizing muscle relaxants.¹ A life-threatening clinical picture can rapidly evolve, characterized by rhabdomyolysis, lactic acidosis, hyperthermia, disseminated intravascular coagulopathy, and lethal cardiac arrhythmias.^{2,3} MH susceptibility (MHS) is conferred by specific inherited mutations, most commonly related to the ryanodine receptor involved in the excitation-contraction process of the muscle cell.³⁻⁵ When a MHS patient is exposed to a triggering agent, there is destabilization of intracellular calcium regulation resulting in acute MH syndrome.¹

The muscular dystrophies encompass a diverse group of disorders with varying modes of inheritance and pathophysiological characteristics. The most prevalent are the X-linked recessive types, Duchenne

muscular dystrophy (DMD) and Becker dystrophy (BD). Numerous publications in the anesthesia literature have suggested an association between DMD and BD and an increased risk of a MH episode.⁶⁻¹¹

DMD, which occurs in approximately 30 per 100,000 liveborn males, is caused by a recessive mutation on the X-chromosome that prevents normal formation of dystrophin, a muscle-stabilizing protein. Dystrophin is an important part of the dystrophin-glycoprotein complex. The dystrophin-glycoprotein complex is part of a larger complex of proteins associated with dystrophin, which plays a role in sarcolemmal integrity (Figure 1). Loss of dystrophin (partial in BD or complete in DMD) disrupts sarcolemmal integrity and leads to muscular dystrophy.^{12,13}

DMD usually presents in early childhood as weakness and motor delay. Delayed walking beyond 15-month-old is a common initial sign. During development, clinical manifestations include progressive lower extremity weakness, pseudohypertrophy of the calves, and markedly elevated creatine kinase levels. Almost all patients with DMD are symptomatic by the age of 5 yr, with difficulty running, jumping, climbing steps, and a waddling gait. Proximal weakness causes patients to use their arms in rising from the floor (Gower's sign). Progressive and severe muscle atrophy and weakness cause loss of the ability to ambulate by the age of 14 yr. Cardiac disease in both DMD and BD manifests as a dilated cardiomyopathy and/or cardiac arrhythmias. Approximately, one third of the patients with DMD develop cardiomyopathy by the age of 14 yr and almost all patients have

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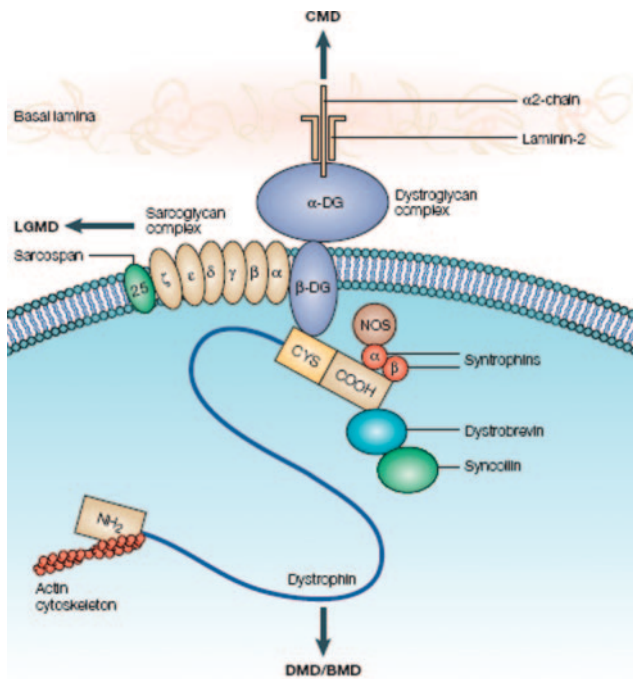


Figure 1. Schematic representation of the organization of the dystrophin-glycoprotein complex (DGC). Various muscular dystrophies (MD) result from defects in the muscle DGC. DMD results from a complete deficiency of dystrophin, whereas a partial deficiency leads to BD. Deficiency in laminin leads to congenital muscular dystrophy and defective glycosylation of the α -dystroglycan leads to limb-girdle muscular dystrophy. BMD = Becker muscular dystrophy; CMD = congenital muscular dystrophy; CYS = cysteine; DG = dystroglycan; DMD = Duchenne muscular dystrophy; LGMD = limb-girdle muscular dystrophy; NOS = nitric oxide synthase. (Adapted with permission from Khurana TS, Davies KE, *Nat Rev Drug Discov*, 2003, 2, 379–90.)¹²

cardiomyopathy by the age of 18 yr. Patients with DMD ultimately die in early to midadulthood secondary to a progressive cardiomyopathy and/or ventilatory pump insufficiency.

BD, which occurs in approximately 3–6 per 100,000 male births, is an X-linked recessive inherited disorder that is similar to DMD (progressive muscle weakness of the legs and pelvis), but progresses at a slower rate because of a partial loss of dystrophin. Symptoms usually appear in early adolescence, but may begin later. BD patients can present with cardiomyopathy, which is not consistent with their skeletal muscle weakness. Most patients will have cardiomyopathy by 30 yr of age. Mortality in BD patients typically occurs between 30 and 60 yr from respiratory failure or cardiomyopathy. DMD and BD carrier females may either be asymptomatic or have mild musculoskeletal symptoms, but are at risk of dilated cardiomyopathy. The accuracy of genetic testing in diagnosing DMD and BD is rapidly improving.

The risks related to anesthesia and sedation for patients with DMD include potentially fatal reactions to certain anesthetics, upper airway obstruction, hypoventilation, atelectasis, congestive heart

failure, cardiac dysrhythmias, respiratory failure, and difficulty weaning from mechanical ventilation. Preoperative evaluation in patients with DMD and BD should include a detailed work-up of their pulmonary function, which includes measurement of forced vital capacity, maximum inspiratory pressure, maximum expiratory pressure, and peak cough flow.¹³ Preoperative training with assist devices should be considered based on their pulmonary function.¹³ Complete cardiac evaluation should be undertaken before any surgical procedure and a dobutamine stress test should be considered if any abnormalities of cardiac function are present. Medical therapy of any cardiac dysfunction should be optimized before any surgery.¹⁴

Myotonic dystrophy, an autosomal dominant disorder, characterized by myotonia, weakness of facial and anterior neck muscles, a progressive distal to proximal weakness of the limbs, and involvement of other systems, will be discussed in a separate article in this series of reviews.

We undertook this systematic analysis of the pertinent literature with the purpose of defining the association between DMD and BD, and MHS, and to describe additional anesthesia-related complications.

METHODS

We performed a literature search using PubMed, Medline, OVID, and ISI using the search terms “malignant hyperthermia,” “muscular dystrophy,” “Duchenne,” “Becker,” “myopathy,” “rhabdomyolysis,” and “cardiac arrest,” and crossreferenced all with the term “anesthesia.” All languages were included but only reviews of abstracts of non-English language studies were possible. References of identified literature were explored, and identified authors were used as additional search terms.

RESULTS

One hundred seventy-three references were identified and reviewed by the authors. Nearly all involved DMD or BD, and thus, the subsequent discussion will be focused on these specific disease entities.

After an initial review of these published cases and studies, and by consensus of the authors, we broadly identified four categories of anesthetic complications in patients with DMD and BD: disease-related (DMD) intraoperative heart failure, rhabdomyolysis and hyperkalemic cardiac arrest in the absence of succinylcholine administration, acute hyperkalemia after administration of succinylcholine, and MH. Postoperative respiratory failure is also a known contributor to perioperative morbidity and mortality in patients with DMD, but has been recently addressed elsewhere.¹³

Intraoperative Heart Failure

Most retrospective reports on the anesthetic management of patients with DMD attest to the safe use of

inhaled volatile anesthetics without succinylcholine.^{15–18} Nevertheless, there are several reports of intraoperative heart failure attributable to ventricular insufficiency in patients with known DMD during correction of spinal scoliosis.^{16,19–22} Characteristic of each was the sudden onset of a nonviable tachyarrhythmia and/or hypotension. The eventual contribution of the general anesthetic agents to the cause of the event cannot be ascertained because events occurred during IV and inhaled anesthetic exposures, without succinylcholine. Gross perturbations of serum electrolytes were not found; however, continuing intravascular volume resuscitation was an aspect of each procedure. In most cases, markers of adequate volume status just before the onset of the event were identified, but the case reports fail to identify whether the volume administered was transiently insufficient considering continuing losses or if the volume loss overstressed an already compromised left ventricle.

Hemodynamic alterations are imposed by prone positioning, positive pressure ventilation, anesthetic exposure, and blood loss.^{13,23} Preoperative echocardiographic assessment of cardiac function and use of invasive monitoring would appear critical to the successful management of these patients.⁷

Rhabdomyolysis in the Absence of Succinylcholine

Intraoperative and postoperative cardiac arrests as a result of rhabdomyolysis and hyperkalemia have occurred in patients with DMD and BD in the absence of succinylcholine administration.^{7,24–27}

We identified seven cases of rhabdomyolysis and intraoperative cardiac arrest secondary to hyperkalemia during the use of inhaled anesthetics in patients with DMD.^{8,28–32} Halothane was the anesthetic in all cases. The muscular dystrophy status of the patients was not known in three of these cases.^{8,29,31} Bradycardia and tachycardia were both observed to precede complete cardiovascular collapse. The time of onset of the clinically significant cardiac arrhythmia after anesthetic induction was variable. Cardiac arrest occurred in some cases with minimal anesthetic exposure, either shortly after induction or during the early portion of the procedure. Initial serum potassium levels exceeded 8 mEq/dL in four patients with no documentation in the other three. Resuscitations persisted in excess of 60 min, with full recoveries obtained in six patients. Dantrolene was often used empirically after documented concomitant metabolic and respiratory acidosis, with or without modest temperature increases. These cases would suggest a predisposition to rhabdomyolysis on exposure to volatile anesthetics regardless of surgical stress. The components of an effective resuscitation are difficult to discern but reduction of the serum potassium is crucial.

We identified eight patients with DMD who developed cardiac arrest secondary to rhabdomyolysis and hyperkalemia in the immediate postoperative period after an uneventful intraoperative course.^{10,33–38} The

diagnosis of DMD was not known in three patients.^{34,36,38} One patient was a female DMD carrier.³⁷ Nondepolarizing muscle relaxants were used in three patients and reversal drugs administered in two. Inhaled anesthetics included isoflurane, halothane, and sevoflurane. In each case, the patients arrived to the recovery unit awake and hemodynamically stable, only to abruptly develop cardiac arrest shortly thereafter. Four patients survived; two achieved return to baseline function. Four events were fatal. Marked hyperkalemia and metabolic acidosis was consistently identified during the resuscitation, with serum potassium levels in excess of 8 mmol/L in six patients with no documentation in the other two. One patient rapidly responded to defibrillation, but most resuscitation exceeded 45 min to a maximum of 3 h. In these patients, a clear precipitant rhythm or event was difficult to discern.

We identified three patients with BD from 2.5 to 18 yr, who developed anesthesia-related cardiac arrest.^{28,34,35} One cardiac arrest occurred intraoperatively and two occurred in the recovery room. One arrest was fatal and the other two resulted in prolonged morbidity. All patients received dantrolene sodium to treat hyperkalemia from presumed MH. However, a diagnosis of MH is unlikely because of the absence of a hypermetabolic state preceding the rhabdomyolysis and hyperkalemic event.

In the two patients who survived, the diagnosis of BD had been established before exposure to the inhaled anesthetic. The patient who had a fatal outcome had a family history of BD that was elicited after the crisis occurred and was confirmed in a postmortem muscle biopsy. Because of the delayed appearance of signs and symptoms of patients with BD, it is possible that undiagnosed patients have undergone anesthesia without untoward complications.

Rhabdomyolysis and Life-Threatening Hyperkalemia After Succinylcholine Administration

We identified 37 patients with previously unrecognized DMD who developed succinylcholine-induced hyperkalemic cardiac arrest.^{17,39–61} The majority of these patients did not manifest clinical signs or symptoms of a myopathy at the time of the succinylcholine administration, and therefore, the adverse event led to the eventual diagnosis of a myopathy. The mortality rate in this group of patients was 30%.

Do Muscular Dystrophy Patients have an Increased Risk of MHS?

Clinical suspicion of MH has been reported in patients with DMD and BD.^{6,35,45,62} Nine patients with DMD developed unexplained hyperthermia and tachycardia related to the use of halothane,^{15,56} and six patients had significant rhabdomyolysis without hyperkalemia.^{24,26,27,49,50,63} A majority of these patients had a diagnosis of muscular dystrophy at the time of the anesthetic. In two patients, the symptoms abated after

the volatile anesthetic was withdrawn. Dantrolene was used in some patients because of suspicion of MH.^{26,31,34,35,42,49} However, the rhabdomyolysis and other clinical characteristics that result from administration of succinylcholine and volatile anesthetics to patients with DMD share signs similar to those arising from a true MH episode; thus, the two entities are difficult to distinguish. The clinical presentation of an episode of MH can be variable and some patients may not demonstrate significant rhabdomyolysis or even lactic acidosis. It seems unlikely that there is a true genetic association between DMD and MH because the genetic mutation associated with DMD is located on the X chromosome, and the mutations associated with MHS are usually found on chromosome 19. Nevertheless, some patients with DMD have demonstrated a positive caffeine-halothane contracture test indicating MHS.^{6,35,55,62,64} The validity of a caffeine-halothane contracture test in patients who have muscular dystrophy has been debatable as the muscles in these patients may be prone to a positive test on exposure to triggering agents.⁶⁵⁻⁶⁷ However, in all these "clinical MH" cases, the patients suffered acute rhabdomyolysis with hyperkalemia without other classic signs and symptoms of MH, and did not have any evidence of hypermetabolism, which is a hallmark of MH.^{1,2}

Although muscular dystrophy patients are unlikely to have an increased risk of MHS, exposure to volatile anesthetics may be associated with life-threatening rhabdomyolysis and therefore should be used cautiously and when the benefits of their use outweigh the possible risks. Undiagnosed motor delay or loss of motor milestones should prompt neurological evaluation before administration of general anesthetics.

Possible Mechanism of Anesthetic-Induced Hyperkalemia in DMD/BD

The pathophysiology underlying the development of inhaled anesthetic-induced rhabdomyolysis in patients with DMD and BD is not precisely known. It is possible that, in dystrophic patients, inhaled anesthetics exacerbate breakdown of already frail and vulnerable muscle membranes that are further disrupted by patient movement or administration of reversal drugs.⁶⁸ It was speculated that calcium regulation might be deranged in the dystrophic muscle.⁶⁹⁻⁷¹ There are signs of altered membrane permeability, such as elevated levels of muscle-specific cytoplasmic proteins (e.g., creatine kinase), in the serum of patients with DMD and BD.⁶⁹

There are two general mechanisms underlying succinylcholine-induced hyperkalemia: excess potassium release as a result of up-regulation of abnormal extrajunctional acetylcholine receptors (e.g., burns, denervation, atrophy, etc.) and development of hyperkalemia as a result of rhabdomyolysis that occurs in patients with clinically evident, as well as subclinical, myopathic disease states, such as DMD.⁷²⁻⁷⁴ Muscular

dystrophy patients may not demonstrate up-regulation of abnormal extrajunctional acetylcholine receptors.⁷⁴ All these patients required prolonged resuscitation. One speculation is that the prolonged resuscitation was in response to continuous and prolonged leakage of potassium from the muscle cells secondary to rhabdomyolysis.⁷²

Succinylcholine should not be administered to patients with known DMD or BD unless required as a last resort for a life-threatening airway emergency, when IV access has not been established. All children presenting for administration of general anesthesia or sedation should be screened for motor milestones. Inability to walk past 18-month-old or other signs of motor loss or delay should prompt suspicion of a subclinical myopathy and should warrant neurological evaluation and genetic testing before elective surgery.⁷⁵ Most cases of DMD and BD will be detected by genetic testing.

CONCLUSION

We did not find an increased risk of MHS in patients with DMD or BD. Exposure to volatile anesthetics in patients with muscular dystrophy may be associated with life-threatening rhabdomyolysis and therefore should be used cautiously, and when the benefits of their use outweigh the possible risks. Succinylcholine administration is associated with life-threatening hyperkalemia and should be avoided in patients with DMD and BD.

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