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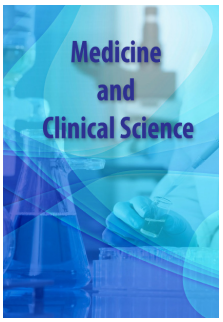
Mini Review




# Preoperative considerations and recommendations for anesthetic management in patients with Duchenne dystrophy disorders

**Marina A Delgado[1,2], Luana A Ferreira[2], Felipe JM Oliveira[1], João Paulo L C Pereira[1], Igor A Procópio[1] and Iara T Araújo[1]**

[1]*Hospital das clínicas de Belo Horizonte, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*

[2]*Programa de pós graduação em ciências da saúde, Santa Casa de Belo Horizonte Ensino e Pesquisa, Belo Horizonte, Minas Gerais, Brazil*

Correspondence

Marina A Delgado

*Hospital das clínicas de Belo Horizonte, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*

E-mail: marina.ayres.delgado@gmail.com
Tel: +55(31)99198-7558

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**Abstract**

Duchenne muscular dystrophy (DMD) is caused by the lack of functional dystrophin protein. Improvements in patient care and disease management may increase the quality of life, but currently, there is no treatment to stop the relentless loss of muscle tissue and function. This condition is associated with life-threatening perioperative complications including heart failure, respiratory insufficiency, rhabdomyolysis, and hyperkalemia. We reviewed the relevant literature about the preoperative evaluation and the safer anesthetic techniques used in patients with DMD. This article presents a short review of the anesthetic procedures to be followed in patients with DMD.

## Introduction

Neuromuscular disorders encompass a group of conditions that affect the function of muscles as well as motor neurons, peripheral nerves, and neuromuscular junctions. The most common and also the most serious type of muscular dystrophy is Duchenne muscular dystrophy (DMD) [1]. DMD is one of the most prevalent muscular disorders, occurs in approximately 30 per 100,000 live-born males, and is caused by a recessive mutation on the dystrophin gene, located on the X-chromosome that prevents the normal formation of dystrophin, a muscle-stabilizing protein, boys are more frequently affected than girls [2]. Dystrophin is an important part of the dystrophin-glycoprotein complex which plays a role in sarcolemmal integrity. Loss of dystrophin disrupts sarcolemmal integrity and leads to muscular dystrophy [3]. In addition to the lack of dystrophin, occurs increased membrane permeability with consequently increased intracellular calcium due to more permeable calcium channels in the sarcolemma and to calcium release from the sarcoplasmic reticulum. There is an up-regulation of acetylcholine receptors as a chronic denervation state [4].

Is known that female patients with DMD are very rare because DMD is an X-linked recessive disease, however, patients with Turner Syndrome, which has only one X chromosome, and patients with the deletion of exons 51-53 of the dystrophin gene will express the DMD phenotype [5]. Patients with DMD presented with progressive degeneration of skeletal, cardiac, and smooth muscle that begins at 3-5 years of age. The diagnosis is confirmed through muscle biopsy [6]. No medical cure exists for this congenital dystrophy, and the disease has a poor prognosis. Treatment is centered on glucocorticoid therapy, prevention of contractures, and medical care of cardiomyopathy and respiratory compromise. Scoliosis correction and other orthopedic surgeries are the most performed procedures in patients with DMD [7,8], however, they may need to undergo other interventions such as appendicitis, cancer surgery [9,10], tonsillectomy [11], colonoscopy [12], etc. In the case of surgery, complications in the perioperative period can be related to the type of anesthetic used and to perioperative exacerbation of this preexisting disease [13].

## Discussion

The majority of reviews available in the literature address recommendations for the management of DMD, including strategies to better improve the patients quality of life [14], however, patients carrying DMD condition who need surgery usually present potential challenges during anesthetic management, including increased susceptibility to anesthetic agents [7,11], inherent muscle weakness, increased risk of cardiorespiratory depression, and potential for rhabdomyolysis and hyperkalemia and there are just a few recommendations about it [15]. Rhabdomyolysis is a condition

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characterized by the destruction of muscle fibers. As muscle tissues are affected, different substances are released into the bloodstream, affecting the kidneys and urinary system [16,17]. Although developments and changes in anesthetic techniques over recent years have improved, complications during anesthesia in these patients are not uncommon. A lot of information is based predominantly on case reports or small series of patients [14,18].

DMD usually presents in early childhood as progressive and severe weakness, motor delay, and markedly elevated creatine kinase levels [3]. The preoperative evaluation should begin with a detailed history and physical exam [19]. DMD patients have macroglossia, weak upper airway dilator muscles. Sedation and general anesthesia cause relaxation of these muscles, which predisposes to upper airway obstruction [13]. Muenster et al. noted that difficult laryngoscopy was reported in around 3.4% of the cases. The progressive fibrosis of the masseter muscle and the neck muscles limits mouth opening, flexion, and extension of the head [20]. The cardiac disease manifests as dilated cardiomyopathy and/or cardiac dysrhythmias. Cardiomyopathy is characterized by a progressive decline in ejection fraction, and the myocardium display areas of myocyte hypertrophy, atrophy, and fibrosis [19]. These patients often have a dysfunction of the sympathetic nervous system, with consequent elevation of circulating catecholamines [3].

Resting preoperative echocardiogram may not predict the ability of the cardiomyopathic heart to respond to the intraoperative stress associated with major surgical procedures. As well, cardiac fibrosis and diastolic dysfunction can often precede systolic dysfunction. A dobutamine stress echocardiogram may provide additional information. Cardiac magnetic resonance imaging is most reliable for early detection of cardiac pathology before a significant change in ejection fraction, however, it requires considerable patient cooperation, deep intravenous sedation, or even general anesthesia, mainly in children. ECG is mandatory and Holter monitoring is a consideration when dysrhythmias are related [21].

DMD is characterized by weakness of the diaphragm, intercostal muscles, and accessory muscles of respiration, resulting in restrictive pulmonary impairment, decreased complacency, progressive decrease in total lung capacity and vital capacity, inspiratory and expiratory reserve volumes, and tidal volume [1,18,22]. These abnormalities lead to hypoventilation, impaired cough, and consequently atelectasis and respiratory failure [13]. In addition, there may be a ventilation-perfusion imbalance and a decrease in the response to CO2 with the appearance of hypoxia and hypercarbia [23]. The development of chronic respiratory insufficiency in DMD is a known finding, indicating increasing weakness of respiratory muscles, particularly loss of diaphragmatic strength. Additionally, developing scoliosis impairs pulmonary reserve [20].

Before patients with DMD receive general anesthesia or sedation, they should undergo measurement of SpO2 in room air, and measurement of the patient's blood gasometry, spirometer, and chest radiography [3]. DMD patients should undergo measurement of the following lung function parameters to access the risk of pulmonary complications and the need for perioperative and postoperative assisted ventilation [20].

Patients with a vital capacity of less than 30%, forced expiratory volume of less than 25%, and maximal voluntary ventilation of less than 50% will normally require prolonged postoperative mechanical ventilation [13,23].

Several patients may have unexpected major thrombotic events. The mechanisms of coagulation pathology remain obscure, however, some authors have suggested that acute muscle destruction may enhance the imbalance between thrombosis and fibrinolysis [5]. Scoliosis is very common in patients with DMD, secondary to progressive musculoskeletal weakness [8,19]. Progress in the medical management of DMD has resulted in longer survival and DMD patients now require more frequent corrective surgical procedures to improve their quality of life [20]. The risks related to anesthesia and sedation include potentially fatal reactions to certain anesthetics upper airway obstruction, hypoventilation, atelectasis, congestive heart failure, difficulty weaning from mechanical ventilation [3].

Numerous publications in anesthesia literature have suggested an association between DMD and increased risk of a Malignant Hyperthermia (MH) episode [3]. Malignant Hyperthermia is an uncommon pharmacogenetic disorder whose susceptibility is conferred by specific inherited mutations, most commonly related to the ryanodine receptor. The acute malignant hyperthermia occurs when the patient is exposed to a triggering agent as succinylcholine and volatile anesthetics, causing a destabilization of intracellular calcium regulation [3]. It seems unlikely that there is a true genetic association between DMD and MH since the genetic mutation of DMD is located on the X chromosome and the mutations associated with MH are usually found in chromosome 19 [3]. Although some patients with DMD have demonstrated a positive caffeine-halothane contracture test, these patients normally presented with acute rhabdomyolysis with hyperkalemia without evidence of hypermetabolism or other classic signs and symptoms of MH [3]. To avoid future complications serial plasma CK, plasma myoglobin, and urinary myoglobin levels should be measured to detect rhabdomyolysis [15].

Exposure to volatile anesthetics and succinylcholine may be associated with life-threatening rhabdomyolysis and hyperkalemia caused by exacerbate breakdown of already frail and vulnerable muscle membranes, rhabdomyolysis, and excess potassium release as a result of up-regulation of abnormal extra-junctional acetylcholine receptors [3]. Succinylcholine and inhaled anesthetics contract muscles, increase intracellular calcium which further damages the already fragile muscle membrane with the release of intracellular potassium, myoglobin, and increases in CK [4].

Considering that, current recommendations contraindicate the use of succinylcholine and volatile anesthetics, and consider the use of a total IV anesthetic technique, but, the absolute contraindication to the use of volatile anesthetics remains controversial [5]. In certain clinical situations such as a potential difficulty puncturing venous access (e.g., pediatric patients) a short exposure to an inhalational agent for induction of anesthesia can be supported. Nevertheless, as soon as possible, immediate conversion to total intravenous anesthesia is recommended, and the patient should be carefully monitored for signs of rhabdomyolysis since its occurrence is unpredictable [15]. Anyway, it is recommended to use a clean anesthesia machine, similar to that for MH - susceptible patients. This recommendation is based on the fact that minimum concentrations of inhalational agents can

trigger rhabdomyolysis [3].

It is known that no anesthetic agent is out of risk because rhabdomyolysis can be reported with other types of anesthetics, even that one considered non-triggering, for example, propofol, benzodiazepines, barbiturates, and ketamine. Other factors like anxiety, the age of the patient, and prolonged fasting may also contribute to rhabdomyolysis. DMD patients younger than 8 years normally have unstable muscle fibers, still attempting to regenerate, and, for that, are more prone to rhabdomyolysis. In older children, the muscle fibers are reduced and for that, they are less susceptible to rhabdomyolysis, on the other hand, they are more susceptible to cardiac and pulmonary complications [5].

Depending on the type of surgical procedure patients will need general anesthesia, regional anesthesia, or just sedation with monitored anesthesia care. Although there is no evidence-based medicine suggesting the advantage of one technique over another, the avoidance of endotracheal intubation would be beneficial in decreasing the incidence of respiratory complications. In the surgeries where general anesthesia is necessary, appropriate equipment for dealing with the possibility of a difficult airway should be readily available [19].

The agents used for anesthetic induction should be based on the patient's comorbid cardiac condition [19]. During the intraoperative period, many different anesthetic combinations are possible to provide deep sedation. For moderately painful procedures such as muscle biopsies, agents such as propofol can be used carefully to prevent respiratory depression. Similar concerns are raised for opioid-based sedation regimen [3]. During intravenous general anesthesia, propofol is one of the most commonly used agents, to avoid inhalational agents [24]. Dexmedetomidine, an alfa 2 adrenergic receptor agonist agent that has sedative, analgesic, and anxiolytic properties can be used safely as it has limited respiratory depression [24].

Ketamine is a very interesting option due to its analgesic properties, maintenance of airway reflexes a respiratory drive [24]. Some authors have suggested intubation and anesthesia without neuromuscular blocking to avoid postoperative respiratory failure and other complications related to the acetylcholinesterase inhibitors, but this may be a problem since anesthesia without blocking nerve impulse transmission at the myoneural junction might not be suitable for some surgical procedures [10]. It can be expected that the duration of blockade of the nondepolarizing neuromuscular blocking will be prolonged. Muenster et al. demonstrated that the onset time of maximum blockade was significantly prolonged as well as recovery. There are pieces of evidence suggesting the efficacy of sugammadex for the reversal of prolonged blockade of rocuronium [20].

After anesthetic induction and endotracheal intubation, adequate intravenous access and invasive cardiovascular monitoring can be obtained, as indicated, based on the myocardial function, cardiac output, blood pressure [19]. If anesthesia-induced rhabdomyolysis (AIR) is suspected, serum potassium levels should be measured and immediately treated in the case of hyperkalemia. To shift potassium back to the muscle cells, intravenous sodium bicarbonate and insulin should be administered, the patient can be hyperventilated to produce a respiratory alkalosis. Increases of CK should be treated with intravenous hydration and mannitol to avoid renal impairment 15. Dantrolene in the management of AIR has no obvious clinical benefits since the drug's mechanism of action is the inhibition of excessive release of calcium from the sarcoplasmic reticulum (SR) by binding to the ryanodine receptor isoform 1 (RYR1) and the mechanism of AIR involves the breakdown of muscle cell membranes with leakage of cell contents [15].

## Conclusion

All patients with DMD should undergo a detailed pre-anesthetic evaluation whenever it is elective surgery. The responsible medical team must be attentive to follow the anesthetic recommendations here deposited and to the postoperative period of these patients to perform an early diagnosis of rhabdomyolysis and the presence of cardiac dysfunction.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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