Perioperative management of a patient with Becker's muscular dystrophy

H. E. Chen[1], L. Cripe[2], J. D. Tobias[3]

[1]The Ohio State University School of Medicine, Columbus, Ohio, USA

[2]Division of Pediatric Cardiology, Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio, USA

[3]Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA

Corresponding author: [3]J.D. Tobias, Department of Anesthesiology & Pain Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA. Email: Joseph.Tobias@Nationwidechildrens.org

> **Key points**
>
> Common perioperative concerns about progressive neuromuscular disorders include the potential for difficult airway management, co-morbid cardiac disease with alterations in conduction and contractility, reduced pulmonary capacity, rhabdomyolysis, and an increased sensitivity to various anesthetic agents.

Abstract

Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) are progressive neuromuscular disorders resulting from mutations in the dystrophin gene. BMD presents similarly to DMD, but generally has a milder clinical course. Clinical features include progressive weakness beginning in the proximal leg and pelvic musculature with eventual involvement of the upper limb, shoulder, and neck muscles. Muscular degeneration in these areas is often associated with orthopedic complications such as scoliosis requiring surgical intervention. The presence of dystrophin in cardiac, smooth, and skeletal muscle as well as in the brain produces complex multisystem involvement that increases the risk of morbidity and mortality during anesthetic care. Common perioperative concerns include the potential for difficult airway management, co-morbid cardiac disease with alterations in conduction and contractility, reduced pulmonary capacity, rhabdomyolysis, and an increased sensitivity to various anesthetic agents. We present a 19-year-old male with BMD who required anesthetic care for posterior spinal fusion. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

Keywords: Becker's muscular dystrophy; perioperative management.

Introduction

Becker muscular dystrophy (BMD) is a progressive neuromuscular degenerative disorder similar in presentation to Duchenne muscular dystrophy (DMD), but generally with a milder clinical course. This family of muscular dystrophies is inherited in an X-linked recessive pattern and is caused by a deletion in the dystrophin gene, a 2.5 megabase gene on the short arm of the X chromosome.[1,2] The birth prevalence of BMD is approximately 1:18,000 live male births.[3] The clinical course of BMD is generally milder due to the distal location of the deletion in the dystrophin gene, which allows for more functional dystrophin to be present in

the body.[4] Dystrophin is found in skeletal, cardiac, and smooth muscle, as well as in the brain, resulting in the involvement of multiple organ systems. Clinical features of this disorder include progressive muscular weakness and wasting usually beginning in the proximal leg and pelvic muscles with increasing involvement of the muscles of the arms, shoulder and neck. In general, the upper extremity involvement is less than that of the lower extremities. Similar to DMD, pseudohypertrophy of the calf muscles is also frequently seen. Cardiac involvement with disorders of both conduction and contractility occurs in approximately 90% of BMD patients. As with DMD, dilated cardiomyopathy remains the primary cardiac involvement.[5-7] The diagnosis of DMD or BMD should be suspected when a young male fails to achieve age appropriate developmental motor milestones. Diagnosis in the majority of cases is established by DNA testing. There currently is no effective treatment; however, glucocorticoid therapy has been shown to slow disease progression. In the past, the definitive diagnosis was based on muscle biopsy with dystrophin staining; however, DNA testing of the dystrophin gene to diagnose BMD is now widely available.[8-10]

As a result of the underlying neuromuscular weakness patients are at significant risk for the development of orthopedic deformities including scoliosis. A significant number of these patients will require spinal fusion, particularly those who are untreated with glucocorticoids.[10] We present a 19-year-old male with BMD who required anesthetic care during posterior spinal fusion for the treatment of scoliosis. Previous reports of anesthetic care for these patients are reviewed, the end-organ involvement discussed, and options for anesthetic care presented.

Case report

IRB approval is not required at Nationwide Children's Hospital (Columbus, OH) for the presentation of individual case reports. The patient was a 19-year-old, 48 kilogram male presenting for posterior spinal fusion

from T_2 to L_3 for the treatment of scoliosis secondary to BMD. His past medical history was significant for the diagnosis of BMD (in-frame deletion of exon 3), moderate scoliosis (52° dextro-curvature of the thoracic spine), restrictive lung disease, and obstructive sleep apnea (OSA). He was born at 40 weeks via Cesarean section with no prenatal complications and weighed 4.1 kilograms. He began walking at 15 months of age, but had difficulty running and was diagnosed with BMD after a pediatrician noticed his gait and large calf muscles. Genetic testing revealed an in frame deletion of exon 3. At the time of the surgery, the patient had been using a motorized wheelchair for approximately 2.5 years and had been non-ambulatory for several months following a fall and an injury to his right knee. There were no previous surgical procedures or anesthetic care. Current medications included vitamins A, C, D, E and B complex, selenium, magnesium oxide and zinc supplements, and coenzyme Q10. Preoperative physical examination revealed a thin male with a prominent pectus excavatum and moderate elbow contractures. A recent electrocardiogram revealed biatrial enlargement and right axis deviation. Echocardiogram showed no significant structural or functional abnormalities with normal left ventricular function and a normal aortic root dimension. Trivial mitral and pulmonary regurgitation were noted, but overall the exam was limited due to poor echocardiographic windows. Despite normal contractility on the echocardiogram, given the patient's underlying BMD, the cardiology consultant noted that he can be expected to have diastolic dysfunction and would be at high risk for perioperative complications. Pulmonary function testing revealed forced vital capacity (FVC) of 67% predicted, forced expiratory volume in one second (FEV_1) of 59% predicted, forced expiratory flow rate of 44% predicted, and FEV_1/FVC of 73% predicted demonstrating mild to moderate restrictive disease.

The patient was held *nil per os* for 8 hours and was transported to the operating room where routine American Society of Anesthesiologists' monitors were applied. After the application of 50% nitrous oxide in oxygen for 2 minutes, a peripheral intravenous cannula was placed and midazolam (2 mg) was administered intravenously. Anesthesia was induced with etomidate (0.2 mg/kg), fentanyl (2 µg/kg), and lidocaine (1 mg/kg). Following the demonstration of adequate, bag-valve-mask ventilation, rocuronium (0.3 mg/kg) was administered to facilitate endotracheal intubation. Direct laryngoscopy was performed with a Miller 2 laryngoscope blade which revealed a Cormack-Lehane grade 2a view and the trachea was intubated with a 7.0 mm cuffed endotracheal tube. Following endotracheal intubation, a second peripheral intravenous cannula and a radial arterial cannula were placed. Using ultrasound guidance, a double lumen central line was placed in the right internal jugular vein. Anesthesia was maintained with a propofol infusion (75-125 µg/kg/min) titrated to maintain the bispectral index at 40-60 and a remifentanil infusion (0.05-0.3 µg/kg/min) to maintain the mean arterial pressure at 55-65 mmHg. Tranexamic acid (bolus dose of 50 mg/kg followed by an infusion of 5 mg/kg/hour) was administered to limit intraoperative blood loss. Neurophysiological monitoring included both motor and somatosensory evoked potentials. The patient was turned prone onto the Jackson table for the operative procedure. The MAP was maintained at 50-65 mmHg for controlled hypotension to minimize intraoperative blood loss. Heart rates varied from 53 to 109 beats per minute with a normal sinus rhythm. No bradycardia or arrhythmias were noted. The mixed venous oxygen saturation, assessed from the venous blood obtained from the CVP catheter, varied from 68 to 74%. Intraoperative fluids included 1 unit of packed red blood cells, 653 mL of cell saver autologous blood, 1000 mL of 5% albumin and 1800 mL of isotonic crystalloid solution. The estimated blood loss was 1100 mL. At the completion of the surgical procedure,

hydromorphone (1.2 mg) and acetaminophen (1000 mg) were administered to provide postoperative analgesia after the remifentanil infusion was discontinued. The propofol infusion was discontinued and the patient was transported to the pediatric intensive care unit (PICU) and his trachea was immediately extubated to non-invasive ventilation using BiPAP (bilevel positive airway pressure) at 12/6 cmH$_2$O. Postoperative analgesia was provided with hydromorphone administered via patient-controlled analgesia (PCA) and the fixed interval administration of acetaminophen every 6 hours for the initial 24 postoperative hours. On postoperative day 1, he was transitioned off of BiPAP with acceptable arterial blood gas results. He was breathing spontaneously on room air with an oxygen saturation of 94-96%. The hydromorphone PCA was transitioned to oral hydrocodone on postoperative day 3. The remainder of his postoperative course was uncomplicated and he was discharged home on postoperative day 4.

Discussion

Given the complex multisystem involvement of Becker muscular dystrophy, there are several specific perioperative implications which may significantly impact the risk for perioperative morbidity and mortality. The importance of such care is illustrated by case reports of cardiac arrest and death in patients with BMD.[11-13] As with the anesthetic care of all patients, the focus of effective perioperative care begins with the preoperative examination and the identification of end-organ involvement by the primary disease process. Of primary concern to anesthesia providers is the potential for difficult airway management, reduced pulmonary capacity, co-morbid cardiac disease with alterations in conduction and contractility, rhabdomyolysis, hyperkalemia, malignant hyperthermia-like reactions and increased sensitivity to various anesthetic agents.

The first obstacle to providing anesthetic care is the potential for difficult laryngoscopy and endotracheal intubation. In the patient with muscular dystrophy, this

may be caused by involvement and fibrosis of the facial muscles, especially the masseter, which can limit mouth opening. Involvement of the neck muscles can limit flexion and extension. Clinical experience has also demonstrated that patients with the muscular dystrophies may have a higher incidence of micrognathia or microstomia, which may further complicate airway management. In their retrospective review, Muenster et al. reported difficult laryngoscopy in 8 of 232 (3.4%) patients which is significantly higher than that routinely encountered in the pediatric population.[14] These issues should be considered during the preoperative airway evaluation. The necessary equipment including tools for fiberoptic intubation and indirect laryngoscopy should be readily available.[15,16] In general, spontaneous ventilation should be maintained until the ability to bag-valve-mask ventilation is demonstrated. In our patient, these issues did not significantly impact anesthetic management and successful bag-valve mask ventilation and endotracheal intubation was accomplished although the view on direct laryngoscopy was slightly less than optimal (Cormack-Lehane grade 2a view). Airway issues may also impact postoperative care related to the need for postoperative mechanical ventilation, especially following extended procedures in the prone position such as spinal fusion, which may increase the incidence of developing airway or lingual edema. Almenrader et al reported that 10 of 42 patients (23.8%) with non-idiopathic scoliosis required postoperative mechanical ventilation (see below).[17]

Another issue that may complicate airway management in the muscular dystrophy patient is the presence of obstructive sleep apnea (OSA). The OSA seen in muscular dystrophy patients is due to weakness of the upper airway dilatory muscles, which increases airway resistance. These issues may be further magnified by obesity, scoliosis, and the residual effects of anesthetic agents. OSA is often compounded by scoliosis and in a study of sleep-related breathing disorders in patients with Duchenne muscular dystrophy, the apnea-hypopnea index and leg movement index were all seen to be significantly higher in the DMD population.[18] These factors combined with skeletal muscle weakness (see below) may lead to perioperative respiratory failure. General precautions include postoperative monitoring of respiratory function in an ICU setting, tracheal extubation when the patient is fully awake following the dissipation of residual effects of intraoperative anesthetic agents, reversal of residual neuromuscular blockade, and the judicious use of opioid analgesia. Although opioid analgesia is necessary to provide postoperative analgesia, the use of adjunctive agents is suggested to decrease perioperative opioid requirements.[19] In our patient, we chose to use acetaminophen intraoperatively and then administered on a fixed interval basis postoperatively to supplement opioid analgesia. Although, non-steroidal anti-inflammatory agents have also been demonstrated to have an opioid sparing effect, concerns have been expressed following orthopedic surgery given the potential inhibition of platelet function leading to increased bleeding as well as their inhibitory effects on new bone formation.[20] Various regional (neuraxial) anesthetic techniques including epidural and intrathecal opioids have been suggested as an alternative means of providing postoperative analgesia following posterior spinal fusion.[21]

In addition to the potential difficulties in airway management, respiratory involvement is universal in patients with disorders of dystrophin such as BMD. Respiratory failure is a major cause of morbidity and mortality in this patient population and thus deserves attention when planning perioperative care. The American College of Chest Physicians has issued a consensus statement which comprehensively reviews the perioperative respiratory care of patients with DMD.[22] Dystrophinopathies weaken the respiratory muscles, which results in impaired cough and progressive loss of lung capacity to the extent that many

of these patients have pulmonary function testing that is less than 30-40% predicted for their age. The American College of Chest Physicians panel recommended the preoperative measurement of the patient's oxygen saturation in room air using pulse oximetry (SaO_2). The measurement of either the $PaCO_2$ or end-tidal carbon dioxide is recommended if the SaO_2 is less than 95%.[23] Although our patient's SaO_2 was 97% on room air, we still routinely obtain pulmonary function testing to identify more subtle changes in respiratory function. Harper et al. reported that 5 of 20 patients (25%) with an FVC $\leq$ 30% had respiratory complications including adult respiratory distress syndrome (ARDS), respiratory tract infections, and the need for a tracheostomy while complications were noted in 4 of the 25 patients (16%) with a preoperative FVC $\geq$ 30%.[24] The consensus panel from American College of Chest Physicians used these data and suggested a two level risk-assessment scale. They suggest that a preoperative FVC <50% is predictive of an increased risk of perioperative complications while there is a high risk if the FVC is <30% of that predicted. They also suggested the use of these values to determine who would benefit from the use of non-invasive ventilation postoperatively. We have developed a clinical practice at our institution where we routinely transition to non-invasive ventilation following extubation of the trachea. This practice is increasing in various centers.[25] The consensus statement also suggested the preoperative assessment of cough strength and effectiveness by measuring maximum expiratory pressure (MEP) and peak cough flow (PCF). The postoperative use of manually and mechanically assisted cough devices was recommended with a preoperative PCF of less than 270 liters/minute or MEP less than 60 cmH_2O.

As with DMD, a major cause of morbidity and mortality in patients with disorders of dystrophin is cardiac involvement resulting in either conduction disturbances or alterations in function. These changes generally manifest during the 2nd decade of life and may result in mortality as early as the 3rd decade. The main characteristic of the secondary cardiomyopathy is a progressive decrease in myocardial function and a depression of the ejection fraction. Clinical signs and symptoms may be absent early in the disease process. As the disease process progresses, cardiac involvement may manifest as decreased exercise tolerance, dyspnea and the development of an audible S3 and S4 or a mitral regurgitation murmur. Clinical manifestations may be mitigated by the lack of mobility and function related to skeletal muscle involvement resulting in a non-ambulatory state in some patients. Fibrosis and scarring generally proceeds from epicardium to endocardium and usually begins around the posterior mitral valve apparatus and spreads progressively towards the apex.[26] Contraction and relaxation abnormalities such as areas of akinesis or dyskinesis, LV posterior wall thinning, LV dilation and decreased ejection fraction can also be appreciated in muscular dystrophy patients. Many patients will be noted to have an abnormally fast average heart rate for age, defined as a heart rate greater than 100 beats/minute in patients $\geq$ 12 years of age.[27-30] This disordered automaticity is related to dysfunction of the autonomic nervous system characterized by an increase in sympathetic activity and a decrease in parasympathetic activity. This predominance of sympathetic innervation in patients with BMD has been suggested as a precipitating factor in arrhythmogenesis, ventricular arrhythmias and sudden death. Additional conduction and rhythm disturbances have also been reported in dystrophinopathies.[7] These have included sinus arrhythmia, sinus pauses, atrial ectopic beats, atrial ectopic rhythm, junctional rhythm, atrial flutter and ventricular premature beats (uniform, multiform, bigeminal and repetitive). Disorders of conduction have included abnormal intra-atrial or interatrial conduction, Mobitz type I block, non-conducted atrial premature beats, short PR interval, right ventricular conduction delay and rightward axis compatible with left posterior fascicular block. Given the invariable cardiac

involvement of Becker muscular dystrophy, preoperative consultation with cardiology is suggested when planning anesthetic care, especially for major surgeries such as scoliosis repair. Whenever feasible, it is recommend to perform major surgical procedures such as scoliosis repair early in the patient's life before the onset of significant cardiac dysfunction. Pre-operative physical exam should begin with measurement of vital signs including weight, blood pressure and heart rate. Additional work-up should include an echocardiogram and electrocardiogram obtained as close to the scheduled surgery date as possible, in order to allow the most up-to-date information to be available to the surgical and anesthesia teams. While echocardiography has long been the preferred imaging modality, cardiac MRI is rapidly emerging as the new imaging modality of choice as echocardiograms are often limited by poor acoustic windows that hinder image interpretation. Early in the disease process, systolic function as assessed by echocardiography may be normal; however, it should generally be assumed that diastolic dysfunction is present even early in the disease process. This involvement may necessitate a higher than normal central venous pressure (CVP) to ensure an adequate cardiac output. Given the potential for altered myocardial function, we chose to use etomidate for anesthetic induction rather than propofol. Although its use in the ICU setting has diminished given its effects on adrenal function in the critically ill ICU patient, etomidate's minimal effects on myocardial contractility makes it an appropriate choice for anesthetic induction in this patient population.[31] Intraoperatively, hemodynamic and fluid status should be closely monitored and guided by invasive arterial and central venous pressure monitoring as was performed in our patient. As ongoing monitors of myocardial function such as transesophageal echocardiography are generally not feasible during prone positioning, other indicators of end-organ perfusion and cardiac output such as venous

saturation, lactate or near infrared spectroscopy may be indicated to guide intraoperative therapy. In our patient, we chose to follow venous oxygen saturation and serum lactate concentrations as indicators of the adequacy of cardiac output and tissue perfusion.[32] Fluid administration to increase preload or the use of vasoactive infusions such as milrinone to augment inotropy, improve lusitrophy, and decrease afterload may be indicated for a venous saturation less than 50% (PaO_2 less than 26 mmHg). The reader is referred to reference 33 for a full description of myocardial involvement in patients with disorders of dystrophin.[33] Patients with muscular dystrophies and other neuromuscular causes of scoliosis have significantly greater blood loss during spinal fusion, losing on average, 78% of their blood volume compared to approximately 20% in patients with idiopathic scoliosis.[34] As such, efforts for blood avoidance and conservation should be addressed preoperative and intraoperatively.[35] Strategies to limit blood loss and the need for allogenic transfusions during orthopedic surgeries may include: (1) optimization of preoperative coagulation function, proper intraoperative patient positioning, and maintenance of normothermia; (2) treatment of preoperative anemia and the use of perioperative erythropoietin; (3) discontinuation of non-steroidal anti-inflammatory agents and herbal medications that may affect coagulation function including ginkgo biloba, ginseng and ginger[35]; (4) autologous transfusion therapy including preoperative donation with the use of erythropoietin and intraoperative collection using acute normovolemic hemodilution; (5) intraoperative and postoperative blood salvage; (5) pharmacologic manipulation of the coagulation cascade with anti-fibrinolytic agents including epsilon-aminocaproic acid (EACA) or tranexamic acid; and (6) controlled hypotension. The advantages and disadvantages of these techniques are outlined in reference 36.[36]

After anesthetic induction and endotracheal intubation, adequate intravenous access and cardiovascular monitoring should be obtained as needed. Maintenance anesthesia generally includes total intravenous anesthesia (TIVA) with propofol and a synthetic opioid (remifentanil or sufentanil) being the most commonly chosen regimen. TIVA optimizes the conditions for neurophysiological monitoring using motor and somatosensory evoked potentials which have been shown to decrease the incidence of spinal cord injury during such procedures.[37,38] Although controversial, the prolonged use of volatile anesthetic agents may result in rhabdomyolysis and hyperkalemia.[11,13,39-41] This phenomenon is not related to malignant hyperthermia (MH) as it is generally agreed that the disorders of dystrophin are not associated with an increased risk of MH. It is likely that there is limited risk of such problems during the brief inhalation induction of anesthesia prior to placement of an intravenous cannula. However, given that an intravenous cannula can generally be placed easily without distressing the patient with the use oral midazolam as a premedicant, 50-70% nitrous oxide via mask, and a topical anesthetic cream, there appears to be limited need for the volatile agents.

Theoretical concerns have also been raised with the use of propofol and its effects on mitochondrial oxidative function as there is a known defect in mitochondrial oxidative capacity in the dystrophinopathies.[39] Rhabdomyolysis that has been postulated to be due to disruption of mitochondrial fatty acid oxidation has been reported with prolonged propofol infusion in the Pediatric ICU setting and there is a known defect in mitochondrial oxidative capacity in the muscular dystrophies.[42,43] Despite such concerns, TIVA with propofol and a synthetic opioid remains the most commonly chosen anesthetic regimen. Especially when used in combination, the hemodynamic effects of these agents which can result in a decrease in SVR and depressed myocardial function must be considered especially in patients with co-morbid cardiac disease.

Another area of concern is the choice of neuromuscular blocking agent (NMBA). Regardless of the circumstance or clinical scenario, succinylcholine should never be administered. Succinylcholine will result in rhabdomyolysis and hyperkalemia ending in cardiac arrest. It is our practice to not even have the medication drawn up into a syringe during such cases. A non-depolarizing neuromuscular blocking agent (NMBA) can be administered after successful bag-mask ventilation is achieved. Even when motor-evoked potentials are being used to monitor spinal cord function, a single dose of a non-depolarizing NMBA can be used to facilitate endotracheal intubation. In patients with myopathic conditions such as BMD, it can be expected that the duration of blockade will be prolonged. Using 0.3 mg/kg of rocuronium, Muenster et al demonstrated that the onset time to maximum blockade was significantly prolonged in DMD patients (median: 315; range: 120-465) compared with controls (median or 315 versus 195 seconds) although the peak effect was not.[44] As expected, recovery was significantly prolonged in DMD patients compared with controls at all recorded time points. The median clinical duration was 40.3 minutes (range, 22-89 minutes) in the DMD group. Similar findings have been reported with vecuronium, mivacurium, and atracurium.[45-47] Disease progression may also affect the response to NMBAs as both onset time and duration of neuromuscular blockade were significantly prolonged in adolescent DMD patients when compared to younger patients.[48]

Non-depolarizing NMBA that have vagolytic actions such as pancuronium should be avoided as they may induce and aggravate the pre-existing tachycardia in patients with BMD. Although not yet available in the United States, there is anecdotal evidence to demonstrate the efficacy of suggamadex for reversal of blockade in this setting.[49] Alternatively, endotracheal intubation can be accomplished with a combination of propofol and remifentanil to avoid the need for a neuromuscular blocking agent, although the potential

hemodynamic impact must be considered.[50] Regardless of the agent chosen, they should not be administered until effective bag-valve-mask ventilation has been demonstrated. A prolonged onset time should be expected. Lower than usual doses should be administered to ensure an acceptable duration of action especially for shorter surgical procedures. Ongoing monitoring of neuromuscular blockade with a standard train-of-four is suggested and demonstration of complete reversal is necessary prior to endotracheal intubation.

The disorders of dystrophin including DMD and BMD result in progressive end-organ dysfunction thereby possessing several perioperative challenges. Specific perioperative concerns include the potential for difficult airway management, co-morbid cardiac disease with alterations in conduction and contractility, reduced pulmonary capacity, rhabdomyolysis, and an increased sensitivity to various anesthetic agents. The primary cause of mortality remains cardiac thereby emphasizing the need for a thorough preoperative evaluation of myocardial contractility and conduction. Perioperative respiratory insufficiency may result from pre-existing skeletal muscle weakness, upper airway issues or sensitivity to anesthetic agents. Patients with a significant dimunition in preoperative respiratory function may benefit from a transition to non-invasive ventilation following tracheal extubation. Additional concerns include the potential for morbidity related to choice of anesthetic agents. Increased sensitivity to non-depolarizing neuromuscular blocking agents should be expected while succinylcholine is absolutely contraindicated. Given the increased life expectancy of these patients, their need for perioperative care continues to increase.

References

1. Kunkel LM, Monaco AP, Middlesworth W, Ochs HD, Latt SA. Specific cloning of DNA fragments absent from the DNA of a male patient with an X chromosome deletion. Proc Natl Acad Sci USA 1985;82:4778-82.

2. Ray PN, Belfall B, Duff C, Logan C, Kean V, Thompson MW, et al. Cloning of the breakpoint of an X;21 translocation associated with Duchenne muscular dystrophy. Nature 1985;318:672-5.

3. Emery AE. Population frequencies of inherited neuromuscular diseases - a world survey. Neuromuscul Disord 1991;1:19-29.

4. Beggs AH, Hoffman EP, Snyder JR, Arahata K, Specht L, Shapiro F, et al. Exploring the molecular basis for variability among patients with Becker muscular dystrophy: dystrophin gene and protein studies. Am J Hum Genet. 1991;49:54-67.

5. Melacini P, Fanin M, Danieli GA, Villanova C, Martinello F, Miorin M, et al. Myocardial involvement is very frequent among patients affected with subclinical Becker's muscular dystrophy. Circulation 1996;94:3168-75.

6. Doing AH, Renlund DG, Smith RA. Becker muscular dystrophy–related cardiomyopathy: a favorable response to medical therapy. J Heart Lung Transplant 2002;21:496-8.

7. Perloff JK. Cardiac rhythm and conduction in Duchenne's muscular dystrophy: a prospective study of 20 patients. J Am Coll Cardiol 1984;3:1263-8.

8. Bradley WG, Jones MZ, Mussini JM, Fawcett PR. Becker-type muscular dystrophy. Muscle Nerve 1978;1:111-32.

9. Chamberlain JS, Chamberlain JR, Fenwick RG, Ward PA, Caskey CT, Dimnik LS, et al. Diagnosis of Duchenne and Becker muscular dystrophies by polymerase chain reaction. A multicenter study JAMA 1992;267:2609-15.

10. Bushby K, Finkel R, BirnKrant DJ et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, pharmacological and psychosocial management. Lancet Neurol 2010;9:77-93.

11. Bush A, Dubowitz V. Fatal rhabdomyolysis complicating general anesthesia in a child with Becker muscular dystrophy. Neuromuscul Disord 1991;1:201-4.

12. Thakker PB, Sharma A. Becker muscular dystrophy: an unusual presentation. Arch Dis Child 1993;69:158-9.

13. Poole TC, Lim TY, Buck J, Kong AS. Perioperative cardiac arrest in a patient with previously undiagnosed Becker's muscular dystrophy after isoflurane anaethesia for elective surgery. Br J Anaesth 2010;104:487-9.

14. Muenster T, Mueller C, Forst J, Huber H, Schmitt HJ. Anaesthetic management in patients with Duchenne muscular dystrophy undergoing orthopaedic surgery: a review of 232 cases. Eur J Anaesthesiol 2012;29:489-94.

15. Weiss M, Engelhardt T. Proposal for the management of the unexpected difficult pediatric airway. Paediatr Anaesth 2010;20:454-64.

16. Walker RW, Ellwood J. The management of difficult intubation in children. Paediatr Anaesth 2009;19:77-87.

17. Almenrader N, Patel D. Spinal fusion surgery in children with non-idiopathic scoliosis: is there a need for routine postoperative ventilation? Br J Anaesth 2006;97:851-7.

18. Polat M, Sakinci O, Ersoy B, Sezer RG, Yilmaz H. Assessment of sleep-related breathing disorders in patients with duchenne muscular dystrophy. J Clin Med Res 2012;4:332-7.

19. Schwengel DA, Sterni LM, Tunkel DE, Heitmiller ES. Perioperative management of children with obstructive sleep apnea. Anesth Analg 2009;109:60-75.

20. Li Q, Zhang Z, Cai Z. High-dose ketorolac affects adult spinal fusion: a meta-analysis of the effect of perioperative nonsteroidal anti-inflammatory drugs on spinal fusion. Spine 2011;36:E461-8.

21. Tobias JD. A review of intrathecal and epidural analgesia after spinal surgery in children. Anesth Analg 2004;98:956-65.

22. Birnkrant DJ, Panitch HB, Benditt JO, Boitano LJ, Carter ER. Cwik VA, et al. American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation. Chest 2007;132:1977-86.

23. Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest 1997;112:1024–8.

24. Harper CM, Ambler G, Edge G. The prognostic value of pre-operative predicted forced vital capacity in corrective spinal surgery for Duchenne's muscular dystrophy. Anaesthesia 2004;59:1160-2.

25. Mills B, Bach JR, Zhao C, Saporito L, Sabharwal S. Posterior spinal fusion in children with flaccid neuromuscular scoliosis: the role of noninvasive positive pressure ventilatory support. J Pediatr Orthop 2013;33:488-93.

26. Allen HD, Thrush PT, Hoffman TM, Flanigan KM, Mendell JR. Cardiac management in neuromuscular diseases. Phys Med Rehabil Clin N Am 2012; 23:855-68.

27. Lanza GA, Dello Russo A, Giglio V, et al. Impairment of cardiac autonomic function in patients with Duchenne muscular dystrophy: relationship to myocardial and respiratory function. Am Heart J 2001;141:808-12.

28. Kirschmann C, Kececioglu D, Korinthenberg R, et al. Echocardiographic and electrocardiographic findings of cardiomyopathy in Duchenne and Becker- Kiener muscular dystrophies. Pediatr Cardiol 2005;26:66-72.

29. Vita G, DiLeo R, DeGregorio C, et al. Cardiovascular autonomic control in Becker muscular dystrophy. J Neurol Sci 2001;186:45-9.

30. Akita H, Matsuoka S, Kuroda Y. Predictive electrocardiographic score for evaluating prognosis

in patients with Duchenne's muscular dystrophy. Tokushima J Exp Med 1993;40:55-60.

31. Scherzer D, Leder M, Tobias JD. Pro-con debate: etomidate or ketamine for rapid sequence intubation in pediatric patients. J Pediatr Pharmacol Ther 2012;17:142-9.

32. Walley KR. Use of central venous oxygen saturation to guide therapy. Am J Respir Crit Care Med 2011;184: 514-520.

33. Cripe LH, Tobias JD. Cardiac considerations in the operative management of the patient with Duchenne or Becker muscular dystrophy. Paediatr Anaesth 2013 (in press).

34. Kannan S, Meert KL, Mooney JF, Hillman-Wiseman C, Warrier I. Bleeding and coagulation changes during spinal fusion surgery: a comparison of neuromuscular and idiopathic scoliosis patients. Pediatr Crit Care Med 2002;3: 364-9.

35. Stanger MJ, Thrompson LA, Young AJ, Lieberman HR. Anticoagulant activity of select dietary supplements. Nutr Rev 2012; 70: 107-17.

36. Tobias JD. Strategies for minimizing blood loss in orthopedic surgery. Sem Hematol 2004;41 (suppl)145-156.

37. Van Der Walt JJN, Thomas JM, Figaji AA. Intraoperative neurophysiological monitoring for the anaesthetist - Part 2: A review of anaesthesia and its implications for intraoperative neurophysiological monitoring. South Afr J Anesth Analg 2013;19:197-202.

38. Van Der Walt JJN, Thomas JM, Figaji AA. Intraoperative neurophysiological monitoring for the anaesthetist: Part 1: A review of the theory and practice of intraoperative neurophysiological monitoring. South Afr J Anesth Analg 2013;19:139-144.

39. Hopkins PM. Anaesthesia and the sex-linked dystrophies: between a rock and a hard place Br J Anaesth 2010;104:397-400.

40. Hayes J, Veyckemans F, Bissonnette B. Duchenne muscular dystrophy: an old anesthesia problem revisited. Paediatr Anaesth 2008;18:100-6.

41. Schmitt HJ, Schmidt J, Muenster T. Dystrophin deficiency, inhalational anesthetics, and rhabdomyolysis. Paediatr Anaesth 2007;17:94-5.

42. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med 2003;29:1417-25.

43. Kuznetsov AV, Winkler K, Wiedemann FR, von Bossanyi P, Dietzmann K, Kunz WS. Impaired mitochondrial oxidative phosphorylation in skeletal muscle of the dystrophin-deficient mouse. Mol Cell Biochem 1998;183:87-96.

44. Wick S, Muenster T, Schmidt J, Forst J, Schmitt HJ. Onset and duration of rocuronium induced neuromuscular blockade in patients with Duchenne muscular dystrophy. Anesthesiology 2005;102:915-9.

45. Ririe DG, Shapiro F, Sethna NF. The response of patients with Duchenne's muscular dystrophy to neuromuscular blockade with vecuronium. Anesthesiology 1998;88:351-4.

46. Schmidt J, Muenster T, Wick S, Forst J, Schmitt HJ. Onset and duration of mivacurium-induced neuromuscular block in patients with Duchenne muscular dystrophy. Br J Anaesth 2005;95:769-72.

47. Rosewarne FA. Anaesthesia, atracurium and Duchenne muscular dystrophy. Can Anaesth Soc J 1986;33:250-251.

48. Ihmsen H, Schmidt J, Schwilden H, Schmitt HJ, Muenster T. Influence of disease progression on the neuromuscular blocking effect of mivacurium in children and adolescents with Duchenne muscular dystrophy. Anesthesiology 2009;110:1016-19.

49. de Boer HD, van Esmond J, Booij LH, Driessen JJ. Reversal of rocuronium-induced profound neuromuscular block by sugammadex in Duchenne

muscular dystrophy. Paediatr Anaesth 2009; 19:1226-8.

50. Demirkaya M, Kelsaka E, Sarihasan B, Bek Y, Üstün E. The optimal dose of remifentanil for acceptable intubating conditions during propofol induction without neuromuscular blockade. J Clin Anesth 2012;24:392-7.