A 12 Year-Old Male with Duchenne Muscular Dystrophy for Spinal Instrumentation and Fusion (Scoliosis Repair)

OBJECTIVES:

1. Review the pathophysiology of Duchenne muscular dystrophy.
2. Recognize the anesthetic implications associated with Duchenne muscular dystrophy.
3. Discuss the preoperative assessment to evaluate the progression of this disease.
4. Review the intraoperative management for scoliosis repair in the presence of this disease.
5. Discuss the management of postoperative pain in the setting of acute opioid tolerance.

STEM CASE – KEY QUESTIONS

A 12 year-old, 55 kg male is scheduled for spinal fusion for scoliosis. His medical history is significant for Duchenne muscular dystrophy, which was diagnosed at the age of 3. He has been confined to a wheel chair for nearly 2 years. The only medication he currently takes is metoclopramide. He is a pleasant adolescent and reports that it has become progressively more uncomfortable to remain upright in his chair.

- What is the pathophysiology of Duchenne muscular dystrophy?
- What are the anesthetic implications associated with Duchenne muscular dystrophy?
- What preoperative testing is necessary prior to proceeding with the planned anesthetic and surgical procedure?

His parents are present at the bedside during your preoperative interview. They report that his only other anesthetic was for a muscle biopsy when he was 3 years old. They are extremely anxious as they recount the previous anesthesiologist’s concern for malignant hyperthermia. They would like to know if anesthesia is “safe” for their child.

- Does the child with Duchenne muscular dystrophy have an increased risk for malignant hyperthermia?

The parents are satisfied with your explanation about the safety of the planned anesthetic. However, his mother inquires about the need for an intravenous (IV) catheter while awake, since her son recently had to endure multiple sticks for blood tests in preparation for this surgery. She would like to know if the mask is an option, as one of the nurses suggested.

- How would you proceed with the induction and maintenance of anesthesia?
- What additional monitors are indicated for intraoperative management?
The S-Caine patch was applied and topical anesthesia allowed successful IV catheter insertion. The patient was premedicated with midazolam (0.05 mg/kg IV). The induction of anesthesia proceeded uneventfully with propofol, and the trachea was intubated after administration of rocuronium. General anesthesia was maintained with propofol (100 – 240 mcg/kg/min) and remifentanil (0.1 – 0.9 mcg/kg/min). A right radial arterial line and a right internal jugular central venous line were placed without incident. A Foley catheter was inserted. Temperature monitoring, IV fluid warmers and forced air warmers were used for the duration of the procedure to maintain normothermia. Somatosensory evoked potentials (SSEPs) were monitored by a neurophysiologist. The blood pressure was maintained at a mean arterial pressure between 50 – 80 mmHg and the hemoglobin concentration above 8 gm/dL by obtaining serial measurements. Blood gases were carried out during the procedure guided by intraoperative blood loss and clinical assessment. The SSEPs remained stable. Suddenly you look up at the monitor and notice the heart rate is 220. The electrocardiogram (ECG) shows a narrow complex regular tachycardia. The blood pressure is 72/44.

- What is your differential diagnosis of this tachycardia?
- Would additional studies would you obtain?
- What is the treatment of this arrhythmia? Does the presence of Duchenne muscular dystrophy alter your treatment plan?

The arrhythmia is successfully treated and the blood pressure is back to baseline. You have barely settled back into your chair when all of a sudden the arterial line tracing appears dampened. You quickly cycle the blood pressure cuff to “confirm” and the pressure is now 50/30.

- What is your differential diagnosis?

The estimated blood loss was 1600 ml and he received lactated ringers solution 3900 ml, and 2 units of donor directed packed red cells totaling 700 ml.

He was extubated awake in the operating room, was responding to command and moving all four extremities. In the recovery room, postoperative analgesia was managed utilizing a patient-controlled analgesia (PCA) pump with morphine. The PCA settings were demand dose of 1 mg, lockout interval 6 minutes, and a continuous infusion of 1 mg/hour. However, the patient continued to report a pain score of 10 on the FACES pain rating scale in spite of multiple additional boluses of morphine and fentanyl (25 mcg per dose).

- Describe the development of acute opioid tolerance or hyperalgesia after continuous intraoperative infusion of remifentanil.
- What is effective treatment for hyperalgesia after remifentanil?
- What is the role of dexmedetomidine use for pediatric scoliosis surgery?
PROBLEM BASED LEARNING DISCUSSION

Pathophysiology of Duchenne muscular dystrophy

Muscular dystrophies are a collective group of inherited noninflammatory, progressive muscle wasting diseases. These entities vary greatly in severity of presentation. Duchenne muscular dystrophy is the most common of these conditions. It is an X-linked recessive disorder resulting from deletion mutations in the dystrophin gene resulting in a complete lack of dystrophin in skeletal muscles. The incidence of this defect is 1/3500 live male births. Dystrophin is a large membrane stabilizing protein which helps anchor the contractile components (actin-myosin filaments) to the cell membrane and indirectly to the surrounding extracellular matrix. Without dystrophin, cell membrane integrity is disrupted causing muscle cell sarcolemmal weakening and profound muscle weakness. Female carriers of the gene do not have peripheral muscle weakness, but can show evidence of a dilated cardiomyopathy.

Initial presentation of this disease occurs in early childhood (age 2 to 6 years) as proximal muscle weakness, a waddling gait and frequent falls. Affected muscles become large as a result of fatty infiltration (pseudohypertrophy). A classic difficulty in getting up from the floor is characteristic. Due to proximal muscle weakness, the child must first lean on the hypertrophied calf muscles and push his trunk up with his arms (child uses his hands to “walk up” his body) to achieve the standing position. This maneuver is referred to as Gower’s sign. Plasma creatinine phosphokinase (CPK) levels are markedly elevated reflecting the increased permeability of skeletal muscle membranes. Progressive and severe muscle atrophy and weakness leads to wheelchair dependence early in the second decade of life. Scoliosis is a frequent complication in non-ambulatory children causing discomfort and leading to further respiratory compromise. Death usually occurs between 15 and 25 years of age due to congestive heart failure and/or pneumonia. However, more of these children are now surviving for longer with medical interventions such as home ventilation and steroid therapy.

Cardiopulmonary dysfunction

Respiratory function in Duchenne muscular dystrophy is impaired by chronic inspiratory muscle weakness. The inability to cough effectively results in loss of pulmonary reserve and accumulation of secretions, which increases the likelihood of recurrent pneumonias. The associated scoliosis alters the chest wall compliance and prevents uniform distribution of tidal volume thus causing a restrictive lung disease pattern with decreases in vital capacity and functional residual capacity. The degree of pulmonary compromise in the presence of scoliosis correlates with the angle of the curvature measured by the Cobb method. This is the angle derived by drawing lines parallel to the upper surface of the proximal-end vertebra and the lower surface of the distal-end vertebra; perpendicularly to these lines are drawn and measuring the angles at the point of intersection of the latter lines form the Cobb angle. In general, there are minimal cardiopulmonary symptoms with angles < 50°. As the Cobb angle progresses beyond 65° a reduction in lung volumes
and a ventilation/perfusion mismatch can be observed. In severe cases (>100o) pulmonary hypertension and right ventricular hypertrophy may develop.

Myocardial involvement is frequently present in Duchenne muscular dystrophy. Characteristic changes on the ECG include tall R waves in the right precordial leads, deep Q waves in the left precordial leads, short P-R intervals and sinus tachycardia. Typical cardiac damage starts with myocardial hypertrophy localized at the septum, which leads to conduction defects such as heart block and arrhythmias. This is followed by the development of a cardiomyopathy, cardiac dilatation and a reduced ejection fraction. Echocardiographic findings are consistent with biventricular dysfunction and a dilated cardiomyopathy. As the cardiomyopathy progresses, heart block and arrhythmias can occur with increasing frequency.

**Gastrointestinal system dysfunction**

A pronounced delay in gastric emptying is also present in Duchenne muscular dystrophy patients. In the presence of blunted laryngeal reflexes, gastric hypomotility increases the risk of aspiration pneumonitis. These patients also experience constipation.

**The safety of muscle relaxants and inhalational agents**

In patients with Duchenne muscular dystrophy, succinylcholine causes rhabdomyolysis as evidenced by myoglobinuria, increased levels of CPK, life-threatening hyperkalemia, and occasionally metabolic acidosis. Succinylcholine (and other depolarizing muscle relaxants) is contraindicated in this population.

If needed, non-depolarizing muscle relaxants can be safely administered to patients with Duchenne muscular dystrophy. The dose requirement of non-depolarizers in those patients is similar to that in healthy patients but the effects may last longer. Careful titration of non-depolarizing muscle relaxants based on train-of-four monitoring is recommended. Adequacy of reversal should be thoroughly evaluated before extubation is attempted.

There have been several reports of cardiac arrest due to rhabdomyolysis in children with both known and undiagnosed Duchenne muscular dystrophy after the use of inhalation agents as follows:

1. Previously undiagnosed Duchenne muscular dystrophy under deep halothane anesthesia without muscle relaxant,
2. Known Duchenne muscular dystrophy after an isoflurane anesthetic without succinylcholine use (arrest occurred in the recovery room),
3. Known Duchenne muscular dystrophy after a sevoflurane anesthetic without muscle relaxant (rhabdomyolysis and hyperkalemia in the recovery without a cardiac arrest).
4. Undiagnosed Duchenne muscular dystrophy after the use of both sevoflurane and isoflurane, without a muscle relaxant due to rhabdomyolysis; arrest occurred after extubation,
(5) Undiagnosed Duchenne muscular dystrophy after sevoflurane and a nondepolarizing muscle relaxant; event occurred in the recovery room after extubation.

The precise mechanism of rhabdomyolysis is unclear. However, based on these reports, it appears that in patients with Duchenne muscular dystrophy, the risks associated with the use of volatile agents may not warrant the benefits of their use. In addition, it is essential to inquire about a family history of dystrophinopathies during the preoperative evaluation of young male children.

Preoperative assessment

The preoperative evaluation of a child with Duchenne muscular dystrophy should focus on the progression of the disease and the degree of cardiopulmonary compromise. The severe muscle weakness these patients suffer from, places them at an increased risk for significant postoperative respiratory insufficiency. Pulmonary function tests provide valuable information especially if the child is wheelchair bound. Room air arterial blood gas measurements detect hypoxia and hypo-/hypercapnia. Traditionally, patients with a pre-operative forced vital capacity of 30% or below predicted have a higher incidence of postoperative complications.

These patients should receive a full cardiac evaluation to determine the degree of underlying myocardial dysfunction.

In addition to the above mentioned studies, routine blood chemistries and hemoglobin determinations should be obtained.

Blood loss in pediatric spine surgery is considerably higher in those patients with neuromuscular scoliosis compared with adolescent idiopathic scoliosis, in spite of normal platelet function. It has been suggested that a defect of primary hemostasis in these patients is likely due to impaired vessel reactivity. Therefore, every effort should be made to obtain autologous or donor directed packed red blood cells when possible.

Intraoperative management

Although no definitive genetic link to malignant hyperthermia has been found, for reasons discussed above it is prudent to use a non-triggering technique. The use of inhalation agents for a relatively short period of time may be safe, especially when intravenous access is not available. The use of non-depolarizing neuromuscular relaxants should be monitored carefully since their duration of action may be prolonged in the child with Duchenne muscular dystrophy.

Regardless of the agents selected, careful titration protects against the depressant effects on myocardial contractility, especially in the presence of an underlying cardiomyopathy.

Invasive hemodynamic monitoring should be considered during scoliosis repair and other complex procedures due to the potential for coexisting cardiomyopathy in Duchenne
muscular dystrophy and the potential for significant blood loss and hemodynamic instability.

Some form of spinal cord monitoring is utilized to detect spinal cord ischemia since too much traction can occlude or diminish blood supply to the cord. Some of the monitoring options are the “wake-up” test, SSEP or motor evoked potential monitoring depending on the preference of the surgeon and the neurophysiologist. A complete description of all these techniques is beyond the scope of this discussion. The surgeons in our institution prefer to monitor SSEPs. This is accomplished by stimulating each one of the four limbs separately by electrodes and monitoring the resultant EEG recordings by scalp and neck electrodes.

SSEPs can be affected by changes in temperature, blood pressure, PaCO$_2$ and concentrations of volatile agent above 0.5 – 1 MAC. Other agents such as N$_2$O, opioids, propofol, muscle relaxants and benzodiazepines do not have a significant impact on SSEPs. Therefore, the choice of remifentanil and propofol infusions for maintenance allows minimal interference with SSEP monitoring and easy intraoperative titration tailored to the hemodynamic status. Severe anemia (hematocrit < 15%) can increase latency and thus should be avoided. A latency increase of 10% or more, or a 50% decrease in amplitude are concerning. If these changes occur, the volatile agent concentration should be decreased, blood pressure and PaCO$_2$ should be normalized and the surgeon should be notified if the signal does not return to baseline.

Tracheal extubation should be attempted only when satisfactory reversal of muscle relaxation is achieved, adequate ventilation is present. Tracheal extubation should be performed after the patient is turned supine.

**Diagnosis and treatment of paroxysmal supraventricular tachycardia (PSVT)**

Early recognition, correct diagnosis of the type of tachycardia and prompt treatment are key factors in the successful management of tachyarrhythmias. Most narrow ($\leq 0.08$ sec) QRS complex tachycardias are often atrial or high junctional, whereas most wide QRS complex tachycardias are of ventricular origin. If the patient is hemodynamically stable, a 12-lead ECG may be obtained to confirm the morphology and the presence or absence of P waves.

PSVT is the most common tachyarrhythmia and non-arrest arrhythmia in children and is the most common arrest arrhythmia in infancy. Rates are greater than 220 beats per minute in infancy and greater than 180 beats per minute in childhood. Ability of the pediatric patient to tolerate the arrhythmia depends on underlying disease, initiating factors, and duration of the PSVT.

In the presence of PSVT and a hemodynamically unstable anesthetized patient, then synchronous cardioversion with 0.5 joules/kg initially is indicated. If PSVT persists or recurs after countershock, additional synchronized cardioversion can occur with the dose increased to 1 J/kg then 2 J/kg. If the patient is stable, vagal maneuvers may be the first
line of therapy until IV adenosine is prepared. The initial adenosine dose is 0.1 mg/kg (max 6 mg) rapid IV push. If unsuccessful, the initial adenosine dose is doubled (0.2 mg/kg (max 12 mg) and repeated. If adenosine fails to convert the rhythm to sinus, then cardioversion is indicated as described above. Adenosine causes a temporary atroventricular (AV) nodal conduction block and interrupts reentry circuits that involve the AV node. It has a wide safety margin because of its short half-life.

Amiodarone (5mg/kg over 20 to 50 minutes) or procainamide (15 mg/kg over 30 to 60 minutes) should be considered for PSVT unresponsive to vagal maneuvers and adenosine. When more than one drug that causes QT prolongation is used, extreme caution must be exercised.

Children with Duchenne muscular dystrophy may suffer from an underlying cardiomyopathy and conduction abnormalities may occur in the later stages of the disease. Rhabdomyolysis and hyperkalemia should always be considered as discussed above. In this group of patients, laboratory studies should be obtained to rule out electrolyte abnormalities.

Finally, sinus tachycardia is the most common tachycardia seen in the anesthetized pediatric patient. Some of the causes of sinus tachycardia include pain, hyperthermia, light anesthesia, hypercarbia, hypoxia and hypoglycemia.

**Diagnosis and treatment of remifentanil hyperalgesia**

For postoperative pain control, various choices are available. Intrathecal opioids may be injected by the surgeon into the cerebrospinal fluid under direct vision. Preservative-free morphine (2.5 µg/kg) provides prolonged postoperative analgesia and decreased parenteral opioid requirements for the first 24 hours. Another effective means of postoperative pain control can be provided by PCA opioid administration.

The intraoperative infusion of remifentanil is associated with the development of clinically relevant acute opioid tolerance in adolescents undergoing scoliosis surgery. In one study, cumulative morphine consumption was 30% greater in patients who received an intraoperative infusion of remifentanil while undergoing scoliosis surgery versus those that received intermittent morphine boluses. A relatively large dose of intraoperative remifentanil appears to trigger postoperative secondary hyperalgesia. Experimental studies performed in animals and volunteers have shown that N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine inhibit central sensitization and prevent opioid-induced hyperalgesia. In one clinical study, low-dose ketamine (0.5 mg/kg just after induction, then 5 µg/kg/min intraoperatively and 2 µg/kg/min for 48 hours postoperatively) successfully prevented remifentanil-induced hyperalgesia thus implicating an NMDA pain-facilitator process.
REFERENCES


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