PBLD Table #: 3

Intra-operative metabolic acidosis: An evaluation of a mitochondrial disorder combined with malignant hyperthermia

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Goals:

1. Management of unexpected and profound metabolic acidosis
2. Understand the peri-operative care of a patient with mitochondrial disorder
3. Identify the existing systems for evaluating a patient with possible malignant hyperthermia
4. Discuss possible anesthetic protocols for a patient with malignant hyperthermia and mitochondrial disorder

Case Discussion and Questions:

An 11year old 40kg female with a history of scoliosis, developmental delay, hypotonia, and feeding intolerance presents to the pediatric operating room for a posterior spinal fusion. Her history is significant for back pain, non-radiating, associated with her scoliosis. Her calculated Cobb angle is 55 degrees and progressing, necessitating surgical intervention. She has not had pre-operative pulmonary function testing. Her only medications include vitamins and omeprazole. She has not had previous operations and there is no reported family history of complications while under general anesthesia. Her pre-operative exam is significant for hypotonia. Her vital signs are normal.

1. *What are possible causes for hypotonia and what are your concerns?*

On arrival to the operating room her monitors were placed and she had an uneventful mask induction with sevoflurane. Two peripheral IVs were secured. A maintenance infusion of lactated ringers was begun. Induction included 2mcg/kg fentanyl , 2mg/kg propofol, and no muscle relaxation. Following this, the patient was successfully intubated. Initial post-intubation vital signs are SpO2 100, R 15, BP 121/65, HR 131. A radial arterial line was also

placed following intubation. Motor and somatosensory evoked potentials are also monitored continuously. Taking this into consideration, the anesthetic plan includes a propofol infusion, half-MAC of desflurane, and supplemental narcotics. The patient is positioned and time out is performed just prior to incision. The "time-out" makes you suddenly realize that no pre-operative blood work has been drawn on this patient! An initial blood gas, type/screen and hemoglobin are drawn and sent to the lab for stat results. As incision is made and the dissection begins, blood loss is approximately 100cc after one hour.
After nervously awaiting the results, the blood gas results FINALLY return--- 7.25/49/288/13, hgb 11.2. You look at them in disbelief and wonder:

2. *What is the differential for metabolic acidosis?*
3. *What is your initial step after receiving these results? Are you notifying the surgeon?*

The patient is hyperventilated to an etCO2 of 30mmHg but she is now becoming hypotensive. Her temperature remains the same at 36.8 degrees. After 30 min an additional ABG is drawn. Pondering the cause of the acidosis you decide to draw a lactate level as well. The results reveal a profound acidosis of 7.1/52/276/9 and lactate of 8mml/dl. Again you are stunned by the numbers and reassess the progress of the operation and the anesthetic management. While these thoughts race through your mind the patient develops ventricular fibrillation and her arterial line and pulse oximetry flatten. You notify the team in the operating room and call for help.

4. *How is PALS altered by metabolic acidosis and at which point would you administer bicarbonate?*

Thanks to well organized PALS, the patient is successfully resuscitated, the case is terminated and she is transferred directly to the PICU intubated. The patient continues to do well and is eventually discharged home but not before her parents contact you to ask "What could have caused this to happen and will it happen again the next time she has anesthesia?"

5. *What is your response?*

Her parents are advised to seek genetic counseling because of this unexplained "reaction" to general anesthesia. The work-up reveals a mitochondrial disorder and her family is now told to call your department for recommendations on further anesthetic care.

6. *What are current peri-operative guidelines for caring for a patient with a mitochondrial disorder?*
7. *Would you have planned your anesthetic differently with this new piece of information?*

Further genetic testing also reveals she is heterozygous for a variant of the RYR1 gene, a mutation which she shares with her father. The significance of this variant has yet to be determined by the MH community. Following this revelation, her parents are told once again to call your department for recommendations on the future care of their child.

8. *How and by whom are patients with a possible MH risk evaluated prior to coming to your operating room?*
9. *Now that her genetics are known, should she get definitive MH testing? What tests are confirmatory?*
10. *Should her parents be tested in lieu of testing the patient?*
11. *If this patient presents to your operating room for a procedure how would you care for her knowing she has a mitochondrial disorder as well as an unknown risk of MH?*

Discussion:

Hypotonia

Hypotonia is classified by the "inability to move or maintain posture against forces that stretch the body, mainly gravity." The fully awake hypotonic child will display the following: lie with their extremities extended and abducted, (frog-leg position), have significant head lag and very little resistance to the examiner when pulled from supine to upright, start to slip through the examiner's hands when held under their arms.

Signs of hypotonia of central origin include abnormal head shape or size, decreased level of consciousness, dysmorphic features, hyperreflexia, seizures, apnea, or abnormal sleep-wake cycles. Signs of hypotonia of peripheral origin include an alert and profoundly weak infant with hyporeflexia and atrophic muscles.

Specific causes of hypotonia include: brain tumor/trauma, infection (meningitis, encephalitis), ischemia, metabolic disease (leukodystrophy, inborn error of metabolism, mitochondrial encephalomyopathy, lactic acidosis, spinal muscular atrophy, poliomyelitis, Guillain-Barre syndrome, Bell palsy, myasthenia gravis, and muscular dystrophies

Intra-operative metabolic acidosis

Concerns revolving around a metabolic acidosis that progresses below pH 2.0 include myocardial depression, pulmonary hypertension, reduction in cardiac contractility and peripheral vascular resistance, resulting in hypotension. Anesthetic risks associated with a metabolic acidosis stem from a potentiation of the circulatory depression that can occur with

anesthesia. These patients are also at risk of compounded sedation, from an acidotic state and any residual anesthetic. Additional insults include tissue hypoxia, decreased threshold for ventricular fibrillation and hyperkalemia. Metabolic acidosis is defined as a primary decrease in HCO3- (22-26). It occurs by three mechanisms: 1. consumption of HCO3-, 2. renal or GI wasting, 3. dilution of ECF with bicarb-free solution. Compensation via pulmonary or renal does not achieve a steady state until 12-24 hours, and does not normally return pH to normal. Causes for increased anion gap include: renal failure, DKA, lactic acidosis, errors of metabolism. For non-anion gap: GI or renal losses of HCO3-, dilutional and total parenteral nutrition. Of most concern while in the operating room would be the most acute processes. These encompass observed hypoperfusion, lactic acidosis, hypovolemia, dilution, malignant hyperthermia and mitochondrial disorders. The latter two causes would be rare but significant.

Initial treatments for metabolic acidosis include taking advantage of controlled respirations and allow hyperventilation to decrease PaCO2. If the pH remains below 7.20, bicarbonate is infused at 1meq/kg until the pH is >7.25. However, sodium bicarb is not recommended for resuscitation during cardiac arrest. It may be given for specific treatments of some toxicities (local anesthetics, narcotics, calcium channel blockers and in hyperkalemic cardiac arrest). Adverse effects include hypokalemia, hypocalcemia, hypernatremia, and hyperosmolality.

<u>Guidelines for peri-operative care of the mitochondrial disordered patient</u>

The current guideline for caring for these patients has changed over the last decade. Each of these patients should be evaluated in the pre-op clinic and blood work should include CBC, CMP, liver enzymes, and ammonia levels. The patient's specialists should be notified and the case discussed with them about alterations in medications and if they are at risk for arrhythmias. Pre-operative fasting must be tailored because they cannot endure prolonged periods of fasting and progress to a state of starvation. Clear carbohydrate fluid can be given 3 hours prior to induction and IV dextrose is infused on arrival to the hospital. If normal eating cannot be resumed following surgery, full parenteral nutrition should be started with amino acid supplement. Intra-operative levels of potassium should be checked and fluids without potassium or lactate should be used as these kids are at risk of alterations in their potassium levels.

Intraoperative management is tailored to the needs of these patients—fluid management should continue as previously mentioned. Volatile agents, except desflurane can be used but if using a non-volatile agent may be beneficial. Desflurane has been associated with depletion of vitamin E levels which can worsen neurologic insult. Adverse outcomes following the use of propofol has largely been associated with inadequate fasting pre-op and prolonged infusions. If the patient is appropriately fasted they should not have an excess of fatty acids which can contribute to the propfol infusion syndrome. Short term usage has not been associated with

poor outcomes. Lastly, succinylcholine is contraindicated because of the risk of hyperkalemia and non-depolarizing neuromuscular blockers are avoided because of a risk of prolonged weakness.

Diagnosis of Malignant Hyperthermia

Definitive diagnosis of MH is only by caffeine-halothane contracture test. This is the test performed in the United States, whereas in-Vitro Contracture Testing is performed in Europe. The diagnosis is: “not MH susceptible” if the test is negative. According to the MH association of the United States, this test is only recommended if there is a high suspicion for susceptibility. The contracture test carries almost 100% sensitivity but only 80% specificity.

Alternatively, genetic testing for RYR1 gene sequencing can be performed which does not require a surgical procedure performed at specific MH test centers. However, because not all causative genes have been identified genetic testing is only recommended for specific persons. If testing reveals an RYR1 mutation that has yet to be linked to an MH risk they should still be treated as if they are MH susceptible until a contracture test has been performed.

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