CASE REPORT

Dexmedetomidine and ketamine sedation for a patient with presumed mitochondrial disease and malignant hyperthermia

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ABSTRACT

Mitochondrial disorders and malignant hyperthermia are two co-morbid conditions which present their own anesthetic difficulties. However, the combination of both pathologies in one patient presents a particularly unique problem with regards to anesthetic management and perioperative care. We present the case of a 20-year-old with both a mitochondrial disorder and malignant hyperthermia history. The perioperative implications of these disorders are discussed and options for anesthetic care reviewed.

Key words: Dexmedetomidine; Ketamine sedation; Mitochondrial disease; Malignant hyperthermia; Anesthetic management

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INTRODUCTION

Mitochondrial disorders are a diverse and poorly described group of diseases. More than 100 genetic mitochondrial mutations have been described.[1] Given the heterogeneous nature of these diseases, anesthetic management can be challenging. We present a 20-year-old man with a history of a mitochondrial disorder in addition to malignant hyperthermia (MH). While the anesthetic management of MH is more fully understood, the combination of MH and a mitochondrial disease poses a unique and challenging perioperative situation. We discuss the anesthetic strategy in the presence of these two co-morbid conditions.

CASE REPORT

Institutional Review Board approval for publication of single case reports is not required at Nationwide Children's Hospital. A 20-year-old, 59 kilogram man with a presumed mitochondrial disorder presented for outpatient dental rehabilitation under general anesthesia. While the patient had been clinically diagnosed as having a mitochondrial disorder, no formal testing had been done. His baseline clinical presentation was that of severe developmental delay, epilepsy, diffuse hypotonia, and blindness. All were thought to be secondary to a mitochondrial disorder although no formal testing had been performed. According to the patient's mother, his only experience with anesthesia was for a tonsillectomy at 4 years of age. This previous anesthetic was complicated by a fever up to 106°F and the need for prolonged postoperative mechanical ventilation. The mother was unable to provide a more detailed history and denied any other family history of anesthetic complications. No hospital or anesthetic records were available from his previous anesthetic, but a presumed diagnosis of MH had been assigned.

After discussion with the dental team, it was determined that the procedure could be accomplished using procedural sedation. The patient was transported to the operating room and a 20 gauge intravenous cannula was placed in the left hand without sedation. Standard American Society of Anesthesiologists' monitors were placed. Initial vital signs prior to sedation were blood pressure (BP) 110/65 mmHg, heart rate (HR) 67 beats per minute, respiratory rate (RR) 18 breaths per minute, and oxygen saturation of 98% on room air. Supplemental oxygen (4 liters/min) was administered and end-tidal carbon dioxide ($EtCO_2$) was measured through a nasal cannula.

Dexmedetomidine was administered as a loading dose of 1 μg/kg over 10 minutes followed by an infusion of 1 μg/kg/hour. After completion of the loading dose, the patient was not adequately sedated for the dental examination and the infusion was increased to 2 μg/kg/hour. Additionally, ketamine (60 mg) and midazolam (4 mg) were administered intravenously in divided doses. The dental rehabilitation procedure was started and the patient's vital signs remained stable with the following vital signs: BP 94/60 mmHg, HR 60 beats/minute, RR 20 breaths/minute, and oxygen saturation 100%. The procedure lasted approximately 2 hours and 15 minutes. The dexmedetomidine infusion was continued at 2 μg/kg/hour for the entire procedure. An additional 140 mg of ketamine was administered during the procedure. To provide additional analgesia, 100 μg of fentanyl was also administered. The patient's vital signs remained stable throughout the procedure. Spontaneous respirations were maintained without difficulty and without the need for a laryngeal mask airway or endotracheal tube. As measured by nasal cannula, the $EtCO_2$ varied between 31 and 45 mmHg. A total of seven dental caries were treated and no local anesthetic was administered. The patient was ultimately discharged home approximately 2 hours after the conclusion of the procedure. His postoperative course was uncomplicated.

DISCUSSION

The mitochondria are intracellular organelles responsible for the production of the majority of a cell's energy supply in the form of adenosine triphosphate (ATP). Disorders of the mitochondria, which are typically genetic in origin, may result from defects in electron transport and/or oxidative phosphorylation. The clinical presentations of mitochondrial disorders are varied, affecting almost any organ system. However, symptoms usually originate from tissues with the highest energy requirements such as the brain, heart, skeletal muscle, and retina.[2] This was evident in our patient who presented with severe developmental delay, epilepsy, hypotonia, and blindness.

Mitochondrial disorders, while rare, present significant challenges in anesthetic management. The effects of inhaled and intravenous anesthetic agents on dysfunctional mitochondria are poorly understood.[3] As such, there are limited evidence based recommendations to guide anesthetic practice in these patients. Rafique et al. conducted a survey that showed the diverse array of techniques that anesthesia providers choose in this patient population.[3] Their survey revealed that 18% of practitioners use malignant hyperthermia (MH) precautions for patients with known mitochondrial disorders. While patients with a definitive diagnosis of mitochondrial disease are not thought to have an MH risk[4], those with unspecified hypotonias do pose an interesting challenge. A non-triggering anesthetic may be preferable in a patient with a myopathy, although the agent generally chosen for such cases, propofol may not be ideal in those with mitochondrial disease. Our dilemma was similar in that our patient had both a presumed mitochondrial disorder as well as a history suggestive of MH.

Total intravenous anesthesia (TIVA) with propofol is often considered an ideal, non-triggering anesthetic for patients at risk for MH. However, in the setting of a mitochondrial disorder, a lipid emulsion may overload an already deranged fatty acid oxidation system and result in a clinical picture resembling propofol infusion syndrome (PRIS).[5] Additionally, propofol has been shown to directly disrupt adenosine triphosphate (ATP) production by inhibiting the flow of electrons down the mitochondrial respiratory chain.[6] Characterized by acidosis, rhabdomyolysis, and cardiac failure, PRIS is a rare disorder usually seen after prolonged infusions of propofol in the ICU setting.[7] While the toxic dose is thought to be >4 mg/kg/hours, the tolerable dose in patients with a mitochondrial dysfunction is unknown. Given our patient's history and the likely presence of a mitochondrial disorder, we chose to avoid the use of propofol.

The use of volatile anesthetic agents appears to be safe in the presence of a mitochondrial disorder.[8] However, volatile anesthetic agents have been shown to inhibit respiratory chain function in mitochondria.[9] While the clinical significance of this is not completely understood, it may explain why some patients with mitochondrial disorders have exhibited a significant sensitivity to sevoflurane.[10] A maintenance anesthetic with sevoflurane may have been acceptable for our patient in the absence of the history suggestive of MH.

Dexmedetomidine, an α_2-adrenergic agonist, may be the preferable anesthetic agent in the presence of MH and a mitochondrial disorder. It is generally considered safe in patients with mitochondrial disorders,[1] and has been shown to have beneficial effects on the mitochondrial membrane in ischemic rats.[11] While limited data exists on the use of dexmedetomidine in the presence of MH sensitivity, no interaction has been noted and multiple case reports have demonstrated its safety in that population.[12] Furthermore, the sympatholytic effects of dexmedetomine may incur an added benefit given that catecholamine surges have been implicated in the triggering of MH.[13]

However, potential issues with dexmedetomidine include its failure when used as the sole agent for invasive procedures,[14] and the potential for hemodynamic effects including bradycardia and hypotension.[15] The addition of ketamine allowed us to provide additional analgesia and sedation while attenuating the hemodynamic effects of dexmedetomidine.[16] Similar to the volatile anesthetic

agents, ketamine is widely considered to be a safe anesthetic agent for patients with mitochondrial disorders and MH.[1] However, like the volatile anesthetic agents, ketamine has been shown to depress mitochondrial function in vitro which warrants cautious use.[17] Given the limitations of these two agents, we felt that a dexmedetomidine infusion in combination with supplemental bolus doses of ketamine would provide safe and effective sedation for a dental procedure.

Fentanyl and midazolam were used as adjuncts to dexmedetomidine and ketamine. While both opioids and benzodiazepines can cause respiratory depression and subsequent respiratory acidosis, both are considered safe in the presence of mitochondrial disorders.[8] Furthermore, opiates and benzodiazepines are the two most common intravenous agents used by pediatric anesthesiologists in the setting of mitochondrial disorders.

CONCLUSION

We present an option for anesthetic are in a patient with a past medical history of mitochondrial cytopathy in combination with a questionable episode of MH, both of which made our choice of anesthetic unique and challenging. Given that endotracheal intubation was not necessary for operative dentistry, a decision was made to use an anesthetic technique that would allow for spontaneous ventilation, while achieving proper sedation and minimizing the potential for adverse effects associated with certain anesthetic agents especially in patients with these co-morbidities. A combination of dexmedetomidine and ketamine were used as the primary anesthetic, with each offsetting the unfavorable hemodynamic effects of the other. There was no clinically significant change in cardiovascular or respiratory function even as the dexmedetomidine infusion was increased to 2 μg/kg/hour. Midazolam and fentanyl were successfully used as short-acting adjuncts during more stimulating stages of the procedure. The patient's postoperative course and recovery were uneventful with adequate pain control. Our anecdotal experience and previous reports from the literature suggest that a combination of dexmedetomidine and ketamine provides an effective combination for procedural sedation, particularly in select populations who are at a greater risk of perioperative complications due to underlying co-morbid conditions.

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