

Literature Review

ANESTHETIC CONSIDERATIONS IN PATIENTS WITH MITOCHONDRIAL DISORDERS

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ABSTRACT

Introduction: Mitochondrial Disorders (1/4,000 patients) are rare and caused by dysfunctional mitochondria. Anesthetic consideration in patients with Mitochondrial Disorders involves careful preoperative and perioperative observations. **Objective:** To provide a brief insight into how general anesthetics interfere with mitochondrial energy formation pathways and help form precautions for anesthesiologists when managing patients with Mitochondrial Disorder. **Review:** Mitochondrial Disorder patients would experience various health problems, such as damaged cardiac functions, neurology systems, and musculoskeletal functions due to energy production disruptions by dysfunctional mitochondrial processes. Moreover, patients with Mitochondrial Disorders exhibit hyperreactivity to volatile anesthetics. **Conclusion:** No anesthetic strategies are found to be safe in patients with Mitochondrial Disorder yet. Therefore, anesthesiologists should remain alert when monitoring fluid choices and managing patient temperature with Mitochondrial Disorders.

Keywords: Anesthesia; Anesthetic Consideration; Anesthesiologist; General Anesthesia; Mitochondrial Disorder

ABSTRAK

Pendahuluan: Gangguan mitokondria merupakan salah satu kelainan genetik langka (1/4.000 pasien) yang disebabkan oleh disfungsi mitokondria. Pertimbangan anestesi pada pasien dengan Gangguan Mitokondria meliputi pengawasan ketat pra operasi dan perioperatif. **Tujuan:** Untuk memberikan wawasan singkat tentang bagaimana anestesi umum dapat mengganggu jalur pembentukan energi mitokondria, sehingga dapat diwaspadai oleh para dokter spesialis anesthesiologi saat menangani pasien dengan Gangguan Mitokondria. **Review:** Pasien dengan Gangguan Mitokondria akan mengalami berbagai gangguan kesehatan seperti kerusakan fungsi jantung, sistem saraf, dan fungsi muskuloskeletal akibat terganggunya pembentukan energi oleh proses mitokondria. Pasien dengan Gangguan Mitokondria menunjukkan reaksi hiperaktif (sensitif) terhadap anestesi volatil. **Kesimpulan:** Belum ada strategi anestesi yang aman pada pasien dengan Gangguan Mitokondria. Dokter spesialis anestesi harus waspada daalam menentukan pilihan terapi cairan, dan pengelolaan suhu pada pasien dengan Gangguan Mitokondria.

Kata kunci: Anestesi; Pertimbangan Anestesi; Dokter Spesialis Anestesi; Anestesi Umum; Gangguan Mitokondria

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INTRODUCTION

Mitochondrial Disorders are genetic disorders caused by mutations in mitochondrial DNA (mtDNA). This disease can be passed on from parents to their offspring through

maternal inheritance. It is also clinically heterogeneous, where symptoms primarily impact the central nervous system (CNS), heart, eyes, musculoskeletal, and gastrointestinal systems (1-3). Mitochondrial

Disorder is typically considered a childhood disorder. However, the improvement in genetic laboratory testing has revealed that adult patients can also have mitochondrial disorders. Mitochondrial Disorder patients can endure anesthesia but are at risk for perioperative complications, post-operative ventilation, hemodynamic compromise, and even death (1). No anesthetic strategies have been found to be safe in patients with Mitochondrial Disorders yet (1,2). Therefore, anesthetic consideration for patients with Mitochondrial Disorders is important, and anesthesiologists should be alert when monitoring fluid choices and managing patient temperature.

REVIEW

Mitochondrial Disorder Pathophysiology and Clinical Manifestations

Mitochondrial Disorders can be caused by inheritance from the mother's gene (maternal), through an autosomal recessive or dominant gene, or de novo (4,5). This is because the mitochondrial and nuclear genomes contribute to the mitochondrial proteome (5). Different types of DNA encode the essential structural components of ETC and ATP production via oxidative phosphorylation. Oxidative phosphorylation happens in the inner mitochondrial skin. The three pathways directly involved in the protons pump for intermembrane are complexes I, III, and IV. Complex V also plays a role in the electrochemical gradient to produce ATP from ADP and Pi. Moreover, Mitochondrial Disorders can arise through a multitude of gene mutations. More mutations in mtDNA would explain stronger phenotypic penetrance and manifest in Mitochondrial Disorder.

The strict maternal inheritance of mtDNA results in homoplasmic individuals, who typically have a single mtDNA, the maternal

one. However, heteroplasmy (the simultaneous presence of two or more mtDNA types in the same individual) has often been reported. Mitochondrial DNA spread has higher unpredictability since the mitochondrial genome may be analogous in all copies (homoplasmy) or diverge between copies (heteroplasmy) (1,6). Nevertheless, heteroplasmy has unexpected effects on offspring, and the heteroplasmy rate cannot always correlate with clinical phenotype. Heteroplasmy can primarily occur through somatic mutagenesis during an individual's lifetime and through leakage of paternal mtDNA in the zygote during fertilization (7). Recent studies using modern sequencing techniques have revealed that heteroplasmy from somatic mutations might be prevalent among some individuals. Heteroplasmy and the normal variation in baseline metabolic demand mechanisms explain variable clinical manifestations between individuals. Therefore, we cannot use a generalized anesthetic plan for Mitochondrial Disorder for all patients. Additionally, there is a point at which the cell can tolerate mitochondrial damage. Hence, metabolic dysfunction and symptoms occur after mutations exceed the threshold. For example, the mitochondrial disorder Leigh syndrome is a progressive neurodegenerative disorder that can be caused by 80 different genetic mutations (1,3,8).

A patient is suspected of respiratory chain disorder when they have these risks and exhibit the following symptoms: (1) consanguineous parents; (2) maternal inheritance; (3) more than one affected system; (4) progressive disease; (5) worsening state due to energy imbalance (catabolic states, for example, nausea, diarrhea, dehydration, fever, extended fasting, surgical procedure); or become affected by drugs metabolized at the

mitochondria. The vast symptoms of Mitochondrial Disorder in childhood include epilepsy, encephalopathy, stroke, brain hyperintensities in T2 and FLAIR, sensory neural hearing loss, cardiac hypertrophy, muscle weakness, ophthalmic problems, and tubulopathy (6).

Furthermore, patients with Mitochondrial Disorders do not manifest only one disease; they frequently overlap with multiple syndromes. Mortality typically increases with respiratory failure complications. Patients also generally have acute symptoms or remain stable until triggered by fever, infection, pregnancy, or anesthesia (1). Childhood-onset Mitochondrial Disorder has significantly higher mortality than adult-onset Mitochondrial Disorder. Adult-onset Mitochondrial Disorder is insidious; its symptoms include progressive vision impairment, ataxia, cardiomyopathy, and cardiac impairment. Recently, next-generation sequencing (NGS) has allowed for the diagnosis of genetic mutations by revealing new genetic impairments in more than 300 genes (1,5,8,9).

A muscle biopsy is the gold standard for diagnosing Mitochondrial Disorders (1). Mitochondrial dysfunction is characterized by ragged-red fibers. Analysis can also be conducted for specific mtDNA mutations. However, DNA sequencing is also essential for diagnosis. Patients with Mitochondrial Disorders have genetic mutations in their mtDNA or nuclear DNA or > 70% depletion of mtDNA (for primary mitochondrial depletion syndrome).

Anesthetic Considerations in Mitochondrial Disorder Patients

The anesthetic management of Mitochondrial Disorder patients involves strict

preoperative and perioperative observations. Mitochondrial Disorder patients treated with propofol are not at risk for severe hyperthermia. However, they must not be treated by prolonged propofol infusion as it affects mitochondrial function via multiple pathways. Therefore, propofol use must be restricted. Succinylcholine is also an absolute contraindication because of hyperkalemia and myotonic risks. Non-depolarizing agents must be used with caution, given their random effects. Vein route injection and volatile anesthetics should be gradually infused while observing the patient's clinical symptoms or administered via electroencephalogram (EEG) (1).

Moreover, Mitochondrial Disorder patients have a higher risk of postoperative respiratory depression because of allergies to anesthetics and opioids, pre-existing musculoskeletal conditions, and unpredictable reactions after neuromuscular blocking agents' application. Patients with pre-existing conditions with bad cough reflexes or recurring pneumonia may benefit from using preoperative non-invasive positive pressure ventilation (NIPPV) instead. The protein target hypothesis describes a general anesthetic mechanism through ion channels or receptors. Overall, the different effects between highly varied chemical agents and the adverse events of anesthetics are still debated (1,11).

Preanesthetic Assessment

Mitochondrial Disorder patients typically need surgical treatment for accessory path ablation, a pacemaker, or implanted cardioverter defibrillation (ICD) insertion (1). Mitochondrial Disorder is a chronic condition, so patients must correct their ophthalmology impairment, ear tympany membrane implantation, profound brain stimulation,

gastro-jejunal tubes, fractures surgery, thyroidectomy, or organ transplantation. Before surgical treatment, patients also must pass a holistic assessment, and an interdisciplinary consultation with other specialists is required to build an anesthetic plan.

Next, patients and families are informed about postoperative ventilation risks, mainly for chest or upper abdomen intervention. Neurologic assessments must be documented so the clinician can compare preoperative neurologic deficits and intraoperative events. Neuromuscular changes must also be assessed because of hypotonus, spastic, myoclonic, and rigid muscles. Moreover, clinicians must be aware of the undiagnosed Mitochondrial Disorder in adult patients with pre-existing muscle weakness, especially in increased lactate and multisystem impairments (10). Neuropathy should be examined and documented. The history and management of seizures should be noted to prepare for the patient's ketogenic diet. Additionally, the patient is recommended to continue their antiepileptic drugs until surgery (1).

Furthermore, total anesthesia is strongly favored, as vein sedation brings unnecessary risk. The impaired lung is not the cause of the respiratory disturbance, but neuromuscular and central control of breathing affects by the impaired lung, resulting in respiratory impairment and atelectasis (1). Patients can also have bulbar muscle impairment, difficulty swallowing, stridor and snoring, cough, and hoarseness. Polysomnography can diagnose obstructive sleep apnea (OSA), central apnea, and hypoxia & hypocapnia (2). Children with the disease have also shown sleep-related breathing disturbances. The patient's baseline pulse oximetry and arterial blood gas should

also be checked to assess the baseline carbon dioxide (CO₂) if SpO₂ is under 95% (12).

Hypertrophic cardiomyopathy occurs in 40% of primary Mitochondrial Disorders, and conduction abnormalities are present in >10% of Mitochondrial Disorders. Wolff Parkinson White (WPW), premature ventricular contractions, and preexcitation supraventricular arrhythmias are also present in Mitochondrial Disorders. A complete AV block might happen. Thus, access to external pacing and defibrillation is needed, and a low threshold is required for preoperative pacemaker insertion. Atropine, epinephrine, and isoproterenol should also be available. Before the surgery, patients should do check-ups, especially electrocardiograms and echocardiograms. Invasive arterial blood pressure monitoring is also recommended in Mitochondrial Disorder patients with cardiomyopathy for quick access to blood sampling (1).

Furthermore, Mitochondrial Disorder patients usually have chronic malnutrition, electrolyte imbalances, or growth development impairments, such as growth faltering. Endocrine instabilities are also common, along with diabetes mellitus, adrenal insufficiency, and low thyroid and parathyroid hormone levels (1). Mitochondrial Disorder patients have an impaired ability to use alternative energy pathways in the hypoglycemia state. Therefore, preoperative fasting is limited to 2 hours to reduce glucose depletion, hypovolemia, and overreliance on fat energy pathways. The surgery must be performed as soon as possible to inhibit energy storage usage (1,2).

In some cases, extended fasting can reduce pulmonary aspiration risk; but in Mitochondrial Disorder patients, metabolic and surgical inflammatory stress increases metabolic

impairment and lactate acidosis risks (1). Hence, dextrose infusion added to the perioperative lactate-free infusion is recommended for Mitochondrial Disorder patients. Dextrose is used, except if the patient is on a ketogenic diet or would experience a destructive impact if consuming higher glucose. Normoglycemia must prevent excessive glycolytic oxidation and a rise in the lactate plasma. Additionally, perioperative hemodynamic sustainability and optimum oxygenation are essential to maintain energy formation (13).

Intraoperative Anesthetic Assessment

The intraoperative anesthetic assessment always focuses on reducing metabolic disturbance, sustaining hemodynamics, and enhancing the postoperative respiratory state. Dextrose-based maintenance fluids are recommended, especially for children with Mitochondrial Disorder, to deliver proper energy supplementation (13). In patients with Mitochondrial Disorders, regular glucose level checks should be done. Moreover, as they have weakened lactate metabolisms, lactate in fluids should be evaded. Serum lactate and pH should be checked regularly. Normal saline + 5% dextrose is the choice for maintenance fluid (1).

Temperature instabilities are poorly endured in Mitochondrial Disorder patients. Temperature observations and usage of air and fluid warmers are recommended in the perioperative phase. Shivering depletes energy reserves and causes severe myotonic or paradoxical paralysis. Perioperative complications, such as malignant hyperthermia (MH), affect 1/30,000 children and cause spasms of the musculoskeletal after exposure to volatile anesthetics, such as halothane, resulting in muscle myopathy, acidosis,

arrhythmia, hyperkalemia, hyperthermia, and death (2,14).

Mitochondrial Disorder patients show diaphragm and extra respiratory muscular tissue impairment, which can cause significant respiratory problems. This mechanism can happen rapidly, slowly, or on a progressive pathway. Rapid sequence intubation (RSI) using the muscle relaxant succinylcholine is not recommended because of hyperkalemia and myotonic crisis risks. Thus, anesthetic agents needed to be titrated to minimize hemodynamic disturbance. Inhalation inductions must be conducted slowly and gradually (1).

Processed electroencephalogram (EEG) generates numerical brain electrical activity and prevents inaccurate doses of anesthetics. Processed EEGs and the Bispectral Index (BIS) can help determine specific patient anesthetic depth because of the risk of hypersensitivity to these agents (1,15). Short-acting agents are recommended, and careful observation should be used for patients with respiratory problems and their limited capacity to endure acidosis. Sevoflurane should be better than desflurane and isoflurane because desflurane and isoflurane cause a more significant ventilatory depression. Anesthetic plans that rely on spontaneous ventilation are contraindications, as spontaneous ventilation can cause energy store depletion and airway obstruction. To prevent complications, evaluations to reduce nausea and vomiting, lubrication, and eye protection are recommended. Tourniquets and pressure points are also contraindications due to reduced tissue oxygen delivery (1).

Postoperative Consideration

Postoperative assessment has the same procedure as preoperative assessment. It focuses on sustaining energy and optimizing respiratory functions. Patients with impaired

renal and liver function changes the pharmacologic clearance and postpone recovery from anesthesia. Therefore, careful observation should be done until the patient's status is returned. Pulmonary irrigation, physiotherapy, and prompt mobilization can prevent postoperative atelectasis and help restore muscle strength. Postoperative analgesia is recommended to prevent excess oxygen usage, but clinicians must also ensure that the patient's respiratory and cough mechanisms are safe. Opioid-sparing anesthetics are helpful, and short-acting opioids are recommended (1,12).

Pharmacologic Suggestions

Inhalational Agents

Volatile anesthetics can reduce mitochondrial complex I's ability in vitro (1). On the other hand, general anesthetics (volatile and parenteral) reduce mitochondrial function. Mitochondrial Disorders, especially complex I defect, show hypersensitivity to volatile anesthetics, such as sevoflurane. Research has shown that mitochondrial complex I deficiencies reduce the effective anesthetics dose to half. Meanwhile, imperfections in fatty acid processes do not affect the sensitivity of volatile anesthetics (12).

Volatile agents (halothane, enflurane, isoflurane, desflurane, and sevoflurane) cause anesthetic preconditioning (APC) (2). Previous studies have shown that desflurane has the most significant protective effect of all the volatile agents, followed by sevoflurane and isoflurane. It is also reported that other drugs, such as morphine and lidocaine, have preconditioning properties. Moreover, APC arises if reactive oxygen species (ROS) progress after volatile anesthetics, preventing hypoxia and apoptosis, myocardium ischemic damage, and partial ETC inhibition, resulting in low numbers of

oxidative stress in complex I (sevoflurane), or complex III (isoflurane) (16).

Mitochondrial Disorder patients have an allergy to volatile anesthetics. Regional anesthesia could lessen opioids and other usages. Local anesthetics are suitable for Mitochondrial Disorder patients as there is no clear association between MH and the disease. Reduced end-tidal (ET) sevoflurane dosages are also needed to achieve a loss of consciousness on induction in childhood-onset Mitochondrial Disorders, unlike the typical value of 3.0 until 3.5% sevoflurane needed in healthy children (17).

Volatile anesthetics have rapid elimination, which is beneficial in Mitochondrial Disorders. Volatile anesthetics use exhalation for elimination, allowing an expedient reoccurrence of mitochondrial function after the agent is withdrawn. Thus, low blood/gas solubility drugs, such as desflurane, are beneficial. However, many practitioners avoid volatile agents in Mitochondrial Disorders because of myopathies associated with MH. Nevertheless, the Malignant Hyperthermia Association of the United States (MHAUS) recommends using volatile anesthetics in Mitochondrial Disorder (1,2).

Intravenous Agents.

Propofol damages mitochondrial inhalation by uncoupling oxidative phosphorylation from the ETC, distributing long-chain fatty acids across the cell membrane via acyl transferase I (CPT I), and limiting the production of acetyl-CoA for ATP production via mitochondrial respiration. PRIS occurs at mean doses of more than 4 mg/kg/hour for 48 hours. The symptoms are metabolic impairment, arrhythmias, rhabdomyolysis, hepatomegaly, and dyslipidemia. The PRIS pathophysiology might be caused by

mitochondrial defects in ATP production. Abnormal response to Propofol in children must be screened for the possibility of Mitochondrial Disorder. In Mitochondrial Disorder patients, postponed recovery is seen in patients administered with short-term Propofol. However, in a retrospective review, most of the cohort received Propofol anesthetic without rhabdomyolysis (2,18).

The Mitochondrial Medicine Society (MMS) consensus mentions that Propofol is contraindicated or restricted to short-term use (< 1 hour). Multiple authors elaborate on their research that Propofol induction doses and limited propofol boluses are well tolerated, except in Mitochondrial Disorder patients with a ketogenic diet (18). Patients using TIVA with dexmedetomidine and remifentanyl as non-triggering anesthetic had decreased adverse events associated with mitochondrial stress and metabolic impairment (18,19,20).

The modified-Delphi technique supports the usage of ketamine, barbiturates, midazolam, or other benzodiazepines. Barbiturates, ketamine, and midazolam obstruct complex I activity. Benzodiazepines impact mitochondrial permeability, increasing apoptosis, and barbiturates uncouple oxidative phosphorylation (13,20). Case reports support dexmedetomidine use for continuous infusion or intermittent bolus. However, the recovery was delayed because of prolonged clearance. Thus, the judicious use of these medications is not harmful in a patient with Mitochondrial Disorder (19).

Moreover, opioids are generally well tolerated in these populations. Short-acting opioids or opioid-sparing are suggested. Opioids reduce the propofol dose to achieve a loss of consciousness, unrestrained movement, and hemodynamic responses to noxious stimuli. However, patients may have extra

sensitivity to opioids because of the upregulation of endorphins. Therefore, remifentanyl has been recommended, and the modified Delphi recommends fentanyl as a safe choice for Mitochondrial Disorder patients (21).

Paralytic and Reversal Agents.

Succinylcholine is contraindicated in Mitochondrial Disorder patients due to their common myopathy and myotonic crisis. Hyperkalemia and death can occur because of the upregulation of skeletal muscle nicotinic acetylcholine receptors in Mitochondrial Disorder patients. Thus, close neuromuscular observation (e.g., train-of-four) should be done (1,22).

Neostigmine has shown adverse effects in Mitochondrial Disorder patients and is not an ideal reversal agent. Besides muscarinic side effects, neostigmine triggers a myotonic crisis. On the other hand, sugammadex is a gamma-cyclodextrin that is used in neuromuscular inhibitor reversals. This sugammadex reversal has a beneficial effect: a complete return of paralysis in pre-existing conditions patients. However, further research is recommended to establish safety and dosing recommendations in general Mitochondrial Disorder patients. Total avoidance of neuromuscular blockade is recommended (22).

Local Anesthetics.

Local anesthetics are good for infiltration and periphery nerve blockade. However, bupivacaine use is contraindicated in Mitochondrial Disorder. Bupivacaine affects mitochondrial bioenergetics by disrupting acyl transferase, causing fatty acid beta-oxidation inhibition and the reduction of oxidative phosphorylation. These mechanisms have been proposed as the source of bupivacaine-related

cardiotoxicity across all populations (1). Ropivacaine and lidocaine are favored over bupivacaine due to their minimal inhibition of these biochemical pathways (1,2). Nevertheless, clinicians should administer the minimum dose of ropivacaine and lidocaine to avoid cardiotoxicity in all patients, especially in Mitochondrial Disorder patients (1).

For Mitochondrial Disorders patients with Kearns-Sayre syndrome, neuraxial anesthesia is safe. The anesthetics have been administered without signs of respiratory impairment, hemodynamic instability, or arrhythmia. The main advantages of neuraxial anesthesia are reduced oxygen consumption and acidosis. However, the increased energy demand causes the need to closely monitor the patient's temperature, hydration, and glucose levels (1).

CONCLUSION

Mitochondrial Disorders are rare and are complex multisystem diseases. Anesthetic considerations for Mitochondrial Disorder have resulted in several problems with clinicians. Hence, careful preoperative and perioperative planning is recommended. MMS recommendations are available for safe perioperative Mitochondrial Disorder patients' management. The recommendations include the judicious use of volatile anesthetics while observing the depth of anesthetic drugs. Meanwhile, perioperative optimization is done by reducing fasting, carefully selecting the fluid of choice, and temperature management. Nevertheless, further research is needed to provide more recommendations on anesthetic considerations for Mitochondrial Disorder patients.

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Conflict of interest

The authors declare no conflict of interest.

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Authors' Contribution

All authors have contributed to all processes in this study.

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