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ORIGINAL ARTICLE

Anesthesia for children with mitochondrial disorders: a national survey and review

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Abstract
Purpose Mitochondrial diseases are a heterogeneous group of disorders. Patients with such diseases often need general anesthesia for diagnostic procedures and surgery; guidelines are lacking for the anesthetic care of these patients.
Methods We conducted a survey to investigate the current practices of pediatric anesthesiologists in the US in order to determine and document current practice. The survey consisted of twenty questions, including two demographic questions. A link to the survey was sent via email to members of the Society for Pediatric Anesthesia (2440), and was available online for 14 weeks.
Results Only 503 completed the survey: a response rate of 20.61 %. Among the responders, 93.2 % had children with mitochondrial disorders among their patients, but only 11 % had institutional guidelines for such cases in place. Among the responders, 80.3 % used the standard nil per os (NPO) status guidelines, while the rest give intravenous dextrose solution once NPO was in effect. Only 18.3 % took precautions for malignant hyperthermia during treatment. The majority of the practitioners chose sevoflurane as the safest inhaled agent for induction and maintenance (89.7 and 78.5 %, respectively). Regional anesthesia was deemed safe by 97.3 % of the responders. Lactated Ringer's solution was considered safe for these children by 49 %; only 47.8 % used dextrose-containing fluids for fluid replacement. The blood glucose was monitored by 72.7 %, and the majority (85 %) of this monitoring was done in a postanesthesia care unit.
Conclusion Although the response rate was low, the majority of the responders provide care to these children routinely, so it can be inferred that the results of this survey are the closest published results to the true trend.

Keywords Mitochondrial disorders · Pediatric · Dexmedetomidine · Anesthesia

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Introduction

The mitochondria are intracellular organelles that are responsible for the aerobic generation of adenosine triphosphate (ATP) by oxidative phosphorylation. Mitochondrial disorders, which are caused by a derangement in the production of ATP, are almost always genetic (hereditary vs. mutant) in origin. The defect can occur in the nuclear DNA, the mitochondrial DNA (nDNA or mtDNA), or both.

Mitochondrial disorders have diverse clinical presentations, making it difficult to reach a definitive diagnosis. A very high index of suspicion is needed, as the presentation

can be vague, with longstanding symptoms. The most commonly affected systems are the nervous system, muscles, heart, kidneys, intestines, liver, eyes, and hearing, all of which have high energy demands [1]. The most reliable method of diagnosing and classifying such disorders is to use the modified Walker criteria [2–4]. Diagnostic testing can range from a mere blood test for pre- and postprandial lactate levels to a test that is as invasive as a muscle biopsy performed under general anesthesia (GA) [1]. Anesthesiologists often encounter patients from this unique and challenging population when they undergo diagnostic or surgical procedures needing GA. The effects of potent inhaled anesthetic agents and other anesthetic drugs on the disease processes and clinical courses of these patients are incompletely known. Such a patient is at risk of exacerbating their baseline clinical condition (and possibly metabolic status) during the perioperative period due to their nil per os (NPO) status, surgical stress response, anesthetic agents, or other factors. The current literature is limited to case reports and chart reviews [4–8]. It is important to remember that patients with mitochondrial disease presenting for surgery are a heterogeneous pathophysiological population. The effects of anesthetic drugs on these patients depend not only on the specific mitochondrial enzyme defect present but also factors such as the dose of the drug, the duration of exposure, and comorbidities. We therefore conducted this survey in order to determine and document current practices.

Methods

We conducted a survey, after local IRB and Society for Pediatric Anesthesia (SPA) research committee approval, to determine and document current practices of pediatric anesthesiologists in the United States. After reviewing the literature and institutional guidelines, challenges and controversies were identified and survey questions were developed. The survey consisted of twenty questions, including two demographic questions. A link to the survey was sent via email to SPA members and was available online for 14 weeks. The survey response rate increased when the invitation to participate was repeated, and two reminders were sent at intervals of two weeks. Unfortunately, the SPA did not allow any further reminders. The majority of the responders had patients with mitochondrial disorders in their practice. Among the responders, 60 % had been practicing for more than eight years, so the results could be indicative of the true trend, although the corresponding statistics are rather weak. On the other hand, there could be pediatric anesthesiologists who are not SPA members and are providing anesthetic care to patients with mitochondrial disorders, but the authors did not have a way to contact any pediatric anesthesiologists who were not members of the SPA and include them in the survey.

Results

The total number of survey link recipients was 2440, but only 503 filled in the survey—a response rate of 20.61 %. Among the responders, 93.2 % had children with mitochondrial disorders in their patient population, but only 11 % had institutional guidelines in place for their anesthetic care. The survey questions and results are shown in Table 1.

Discussion

This survey was sent to SPA members, considering they usually anesthetize these patients. The response to the first survey question reaffirmed this assumption; only very few places have formal practice guidelines in place. Sevoflurane and opioids are considered safe by the majority and are included in the institutional guidelines, while propofol, barbiturates, ketamine, dexmedetomidine, and midazolam are preferred in ascending order.

Malignant hyperthermia (MH) is a dreaded complication of GA. Patients with mitochondrial disorders may suffer from myopathies, which can sometimes make practitioners think that the patient has increased susceptibility to MH. Historically, MH was linked with certain muscular dystrophies. It is now known that patients with muscular dystrophies do not have an increased risk of the MH mutation as compared to the general population [9]. The same could be true of patients with mitochondrial disorders, although according to the survey results, some practitioners still take precautions for MH while providing care to these children. This could be considered a safe approach on their part, but it could also inadvertently label these children as being at risk of MH, and make their anesthetic care more challenging.

In response to the questions regarding potent inhaled agents, sevoflurane emerged as the most trusted agent for both induction and maintenance. Inhaled anesthetic agents are known to inhibit the respiratory chain complex [10, 11]. Sevoflurane inhibits the respiratory chain, causing ATP synthase reversal in vitro [12]. Halothane has been linked to arrhythmias in Kearns–Sayre syndrome [5, 8]. However, potent inhaled agents have been used safely in patients with mitochondrial disorders without any reported clinical side effects or exacerbations [4]. At the same time, there is the possibility of increased sensitivity to these agents [13]. The survey results show a very strong trend towards the use of sevoflurane; this could be due to its very common use in

Table 1 Survey questions regarding anesthesia for children with mitochondrial disorders, and results based on feedback from pediatric anesthesiologists

1. Does your patient population include children with mitochondrial disorders and do you provide anesthesia care for these children?	
a. Yes	93.3 %
b. No	6.7 %
2. Is there an institutional policy/practice guideline in place for the anesthetic care for mitochondrial disorder children?	
a. Yes	11.1 %
b. No	88.9 %
3. If yes (an institutional policy is in place) what anesthetic agents are deemed safe or comparatively safe to be used for anesthesia care of these children according to the policy in place? (choose all that apply)	
a. Inhaled agents for induction only	32.9 %
b. Inhaled agents for both induction and maintenance	67.1 %
c. Propofol	37.0 %
d. Ketamine	69.9 %
e. Precedex (dexmedetomidine)	69.9 %
f. Succinylcholine	5.5 %
g. Non depolarizing paralytics	74.0 %
h. Opiates/Opioids	89.0 %
i. Midazolam	76.7 %
j. Barbiturates	42.5 %
4. What is the NPO status policy in your institution for the children with mitochondrial disorders?	
a. NPO according to ASA guidelines with liberal oral fluids till two hours before scheduled procedure	80.2 %
b. NPO according to ASA guideline and IV access with a dextrose solution infusion	19.8 %
5. Do you treat all the patients with "mitochondrial disorder diagnosis" with Malignant Hyperthermia (MH) precautions?	
a. Yes	18.4 %
b. No	81.6 %
6. In your opinion if inhaled agents are considered safe for induction only which agent is preferred? (choose all that apply)	
a. Halothane	3.9 %
b. Isoflorane	4.8 %
c. Sevoflorane	89.8 %
d. All of the above	10.9 %
7. In your opinion if inhaled agents are considered safe for induction and maintenance which agent is preferred? (choose all that apply)	
a. Halothane	1.1 %
b. Isoflorane	29.0 %
c. Sevoflorane	78.6 %
d. All of the above	14.3 %
e. None of the above	5.8 %
8. In your opinion is IV induction with Propofol safe for these children?	
a. Yes	65.1 %
b. No	34.9 %
9. In your opinion what is the non-depolarizing muscle relaxant of choice or considered safest for these children? (choose all that apply)	
a. Atracurium	10.2 %
b. Cisatracurium	33.6 %
c. Rocuronium	33.2 %
d. Vecuronium	20.1 %
e. Pancuronium	4.2 %
f. Only atracurium and cisatracurium	7.3 %
g. Only pancuronium, rocuronium and vecoronium	1.3 %
h. All of the above	33.4 %
i. None of the above	4.9 %

Table 1 continued

10. In your opinion what is the opioid of choice for these children? (choose all that apply)	
a. Fentanyl	47.0 %
b. Morphine	12.3 %
c. Remifentanyl	20.7 %
d. Sufentanil	7.7 %
e. None of the above	1.5 %
f. All of the above	45.9 %
11. In your opinion is regional anesthesia safe for these patients?	
a. Yes	97.3 %
b. No	2.7 %
12. If regional anesthesia is considered safe which local anesthetic agents are safe for these patients? (choose all that apply)	
a. Ester local anesthetics (benzocaine, chlorprocaine, tetracaine etc.)	3.7 %
b. Amide local anesthetics (lidocaine, bupivacaine, ropivacaine etc.)	37.7 %
c. All of the above	60.5 %
13. In your opinion is IV Ringer's Lactate safe for these children?	
a. Yes	49.6 %
b. No	50.4 %
14. Do you monitor/check blood glucose of these patients in the perioperative period?	
a. Yes	72.7 %
b. No	27.3 %
15. If yes to question 14 at what point is the blood glucose measured? (choose all that apply)	
a. Preoperative period	64.4 %
b. Intraoperative	77.3 %
c. Postoperative period in PACU	85.5 %
16. Do you use dextrose containing fluids (D5, D10, D5NS etc.) to replace the losses and maintenance?	
a. Yes	47.9 %
b. No	52.1 %
17. The patients who are on Ketogenic diets how do you manage them?	
a. No special arrangements	53.9 %
b. Overnight admission and IV fluids with dextrose	14.3 %
c. Overnight admission, dextrose free solution and blood glucose/pH monitoring	31.9 %
18. How many years you have been practicing pediatric anesthesia after the residency/fellowship?	
a. 0–4 years	22.4 %
b. 4–8 years	17.3 %
c. More than 8 years	60.4 %
19. Your Practice can best be described as:	
a. Academic setting	63.5 %
b. Private practice	18.0 %
c. Mixed	18.5 %
20. Any additional comments:	

pediatric anesthesia and because it is the agent that is best suited to inhaled induction now that halothane is not available for clinical use in US.

Propofol is known to cause inhibition of the respiratory chain complex [10]. In equipotent doses, propofol and sevoflurane depolarize the mitochondria in vitro; the onset of this effect is rapid with propofol [12]. Propofol is a lipid emulsion intended for clinical use, and its use in patients with fatty acid oxidation disorders could be detrimental [1]. Propofol infusion syndrome (PRIS), a rare but fatal disorder, is usually seen in very sick children receiving long-duration (usually $\geq$24 h) propofol infusion. The hallmark clinical features are cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure. The exact pathophysiology of PRIS is not known, but it is speculated that the effect of propofol on fatty acid metabolism and mitochondrial inhibition could be significant. The current literature suggests that it may be safely used as an induction

agent in a limited number of patients [1, 4, 14], and this could be the reason for its popularity in our survey. Barbiturates are known to inhibit the respiratory chain complex, like propofol [10, 15]. Thiopentol sodium, ketamine, midazolam, and etomidate have been used in these patients without incurring any known adverse clinical effects [4, 16].

Dexmedetomidine, a selective α_2-agonist, is a comparatively new intravenous agent, and has found many uses in anesthetic practice as an adjunct or sole anesthetic with varied success [16–18]. Dexmedetomidine is known to have beneficial effects on the mitochondrial membrane in ischemic rats [19]. The clinical effects of dexmedetomidine combined with these mitochondrial membrane effects make it a very attractive choice for patients with mitochondrial disorders. On the other hand, effects like decreased cerebral blood flow, bradycardia, decreased cardiac index, and effects on blood pressure warrant caution [20]. We should not forget that morphine was found to lower the mitochondrial membrane potential [21] after being clinically available for almost two centuries, so dexmedetomidine is too novel to draw a firm conclusion in this regard. That said, dexmedetomidine is deemed safe and included in the "safe drugs" list in most institutional guidelines.

Opioids are used to control incision pain and have an antinociceptive effect. They can cause respiratory depression, resulting in respiratory acidosis, which could add to baseline metabolic derangements. Morphine (but possibly not other opioids) may have a mitochondrial mechanism of action [21]. On the other hand, morphine, fentanyl, alfentanil, and remifentanil have been used safely in these patients [4]. The survey results indicate that the responders thought that all of the opioids are safe for use in these patients, although a small majority favored fentanyl.

Neuromuscular blockade is an integral part of the balanced general anesthetic technique, and both depolarizing and nondepolarizing neuromuscular blocking drugs are reported to have been safely used in patients with mitochondrial disease [4]. There are reports of increased sensitivity to some (atracurium, rocuronium) [22] and a normal response to others [22–25]. Among these drugs, our survey showed a trend towards the use of cisatracurium and rocuronium by the practitioners.

Patients with mitochondrial diseases may frequently have occult peripheral neuropathy [26]. Local anesthetics have been reported to be used safely in these patients [4, 7]; however, neuraxial blocks should be used with caution, after a thorough assessment of distal neurological status. Local anesthetics are known to disrupt oxidative phosphorylation and decrease bioenergetic capacity in vitro, although the clinical significance of this effect is unknown [27]. Respondents to our survey favored the use of local anesthetics.

The responders were evenly split on the question of whether lactated Ringer's solution should be used, and its safety in this patient population. One of the basic screening tests for mitochondrial disorders is that for pre- and postprandial lactate levels [4, 28]. The load of sodium lactate in lactated Ringer's solution (310 mg/100 ml) could be harmful; the conversion of the sodium lactate to bicarbonate is dependent on the integrity of the cellular oxidative process. The exogenous load of lactate is a potential burden due to the derangements in the respiratory chain in these patients, and can lead to a metabolic decompensation. Other lactate-free isotonic solutions, like normal saline, are safer choices.

There are risks of fasting hypoglycemia in patients with electron transport chain (ETC) disorders, glycogen storage disease, fatty acid metabolism disorders and gluconeogenesis disorders [1], so the use of frequent blood glucose checks and dextrose solution may be warranted. On the other hand, hyperglycemia during the perioperative period is also not without potential harm [29, 30].

The survey was sent to the members on the email list of the Society for Pediatric Anesthesia. There is the possibility that there are pediatric anesthesiologists who are not members of this society, but the authors did not have any way to contact them. Also, the low response rate is an important limitation of this study.

In conclusion, anesthetic agents, both inhaled and intravenous, have depressive effects on the mitochondrial electron transport chain. However, it is important to remember that these pharmacological effects on mitochondria have been studied in healthy cells, not in patients suffering from mitochondrial disorders, so the exact effects of these drugs on diseased mitochondria could be significantly different. It was speculated in the 1970s that mitochondrial electron transport inhibition could explain the anesthetic mechanism, but this did not stand true to the test of scientific discovery [31]. The results of our survey show that the majority of practitioners consider sevoflurane, opioids, dexmedetomidine, midazolam, and local anesthetics are safe for use in children with mitochondrial disorders. More studies are needed before attempts can be made to define the ideal anesthetic for these patients.

References

1. Blm M. Current management in child neurology. 4th ed. Shelton: People's Medical Publishing House; 2008.
2. Thorburn DR, Smeitink J. Diagnosis of mitochondrial disorders: clinical and biochemical approach. J Inherit Metab Dis. 2001;24:312–6.
3. Bernier FP, Boneh A, Dennett X, Chow CW, Cleary MA, Thorburn DR. Diagnostic criteria for respiratory chain disorders in adults and children. Neurology. 2002;59:1406–11.

4. Footitt EJ, Sinha MD, Raiman JA, Dhawan A, Moganasundram S, Champion MP. Mitochondrial disorders and general anaesthesia: a case series and review. Br J Anaesth. 2008;100:436–41.
5. Driessen J, Willems S, Dercksen S, Giele J, van der Staak F, Smeitink J. Anesthesia-related morbidity and mortality after surgery for muscle biopsy in children with mitochondrial defects. Paediatr Anaesth. 2007;17:16–21.
6. Rosaeg OP, Morrison S, MacLeod JP. Anaesthetic management of labour and delivery in the parturient with mitochondrial myopathy. Can J Anaesth. 1996;43:403–7.
7. Hsiao PN, Cheng YJ, Tseng HC, Chuang YH, Kao PF, Tsai SK. Spinal anesthesia in MELAS syndrome: a case with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. Acta Anaesthesiol Sin. 2000;38:107–10.
8. Lauwers MH, Van Lersberghe C, Camu F. Inhalation anaesthesia and the Kearns–Sayre syndrome. Anaesthesia. 1994;49:876–8.
9. Miller RD. Miller's anesthesia. 7th ed. Philadelphia: Churchill Livingstone; 2009.
10. Fleisher LA. Anesthesia and uncommon diseases. 5th ed. Philadelphia: Elsevier; 2005.
11. Hanley PJ, Ray J, Brandt U, Daut J. Halothane, isoflurane and sevoflurane inhibit NADH:ubiquinone oxidoreductase (complex I) of cardiac mitochondria. J Physiol. 2002;544:687–93.
12. Bains R, Moe MC, Vinje ML, Berg-Johnsen J. Sevoflurane and propofol depolarize mitochondria in rat and human cerebrocortical synaptosomes by different mechanisms. Acta Anaesthesiol Scand. 2009;53:1354–60.
13. Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. Anesthesiology. 2002;96:1268–70.
14. Gurrieri C, Kivela JE, Bojanic K, Gavrilova RH, Flick RP, Sprung J, Weingarten TN. Anesthetic considerations in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome: a case series. Can J Anaesth. 2011;58:751–63.
15. Cohen PJ. Effect of anesthetics on mitochondrial function. Anesthesiology. 1973;39:153–64.
16. Koruk S, Mizrak A, Kaya Ugur B, Ilhan O, Baspinar O, Oner U. Propofol/dexmedetomidine and propofol/ketamine combinations for anesthesia in pediatric patients undergoing transcatheter atrial septal defect closure: a prospective randomized study. Clin Ther. 2010;32:701–9.
17. Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha 2 adrenergic receptor. Anesthesiology. 1988;69:818–23.
18. Shukry M, Kennedy K. Dexmedetomidine as a total intravenous anesthetic in infants. Paediatr Anaesth. 2007;17:581–3.
19. Engelhard K, Werner C, Kaspar S, Mollenberg O, Blobner M, Bachl M, Kochs E. Effect of the alpha2-agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. Anesthesiology. 2002;96:450–7.
20. Wong J, Steil GM, Curtis M, Papas A, Zurakowski D, Mason KP. Cardiovascular effects of dexmedetomidine sedation in children. Anesth Analg. 2012;114:193–9.
21. Mastronicola D, Arcuri E, Arese M, Bacchi A, Mercadante S, Cardelli P, Citro G, Sarti P. Morphine but not fentanyl and methadone affects mitochondrial membrane potential by inducing nitric oxide release in glioma cells. Cell Mol Life Sci. 2004;61:2991–7.
22. Finsterer J, Stratil U, Bittner R, Sporn P. Increased sensitivity to rocuronium and atracurium in mitochondrial myopathy. Can J Anaesth. 1998;45:781–4.
23. D'Ambra MN, Dedrick D, Savarese JJ. Kearns–Sayer syndrome and pancuronium–succinylcholine-induced neuromuscular blockade. Anesthesiology. 1979;51:343–5.
24. Wiesel S, Bevan JC, Samuel J, Donati F. Vecuronium neuromuscular blockade in a child with mitochondrial myopathy. Anesth Analg. 1991;72:696–9.
25. Rowe RW, Helander E. Anesthetic management of a patient with systemic carnitine deficiency. Anesth Analg. 1990;71:295–7.
26. Stickler DE, Valenstein E, Neiberger RE, Perkins LA, Carney PR, Shuster JJ, Theriaque DW, Stacpoole PW. Peripheral neuropathy in genetic mitochondrial diseases. Pediatr Neurol. 2006;34:127–31.
27. Muravchick S. Clinical implications of mitochondrial disease. Adv Drug Deliv Rev. 2008;60:1553–60.
28. Fernandes J. Inborn metabolic diseases: diagnosis and treatment. 4th ed. Heidelberg: Springer; 2006.
29. Paut O, Lacroix F. Recent developments in the perioperative fluid management for the paediatric patient. Curr Opin Anaesthesiol. 2006;19:268–77.
30. Hirshberg E, Larsen G, Van Duker H. Alterations in glucose homeostasis in the pediatric intensive care unit: hyperglycemia and glucose variability are associated with increased mortality and morbidity. Pediatr Crit Care Med. 2008;9:361–6.
31. Delogu G, Antonucci A, Moretti S, Marandola M, Tellan G, Signore M, Famularo G. Oxidative stress and mitochondrial glutathione in human lymphocytes exposed to clinically relevant anesthetic drug concentrations. J Clin Anesth. 2004;16:189–94.