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Anesthetic management of 23 procedures in four pediatric patients on an active ketogenic diet
Original Article

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Keypoints

Non-surgical procedures requiring general anesthesia in children on KD are well tolerated, whereas blood pH and glucose analysis should be monitored in procedures longer than 2 hours

Abstract

Objective

To discuss the anesthetic implementations and risks in children who are actively on a ketogenic diet (KD).

Methods

This study is a retrospective medical record review of 23 procedures performed under general anesthesia for 4 pediatric patients on KD during 2020–2022. Demographic data were recorded for the patients, type of anesthesia and procedure, medications used during anesthesia, perioperative complications, duration of anesthesia and KD, and hospital discharge times.

Results

Four children underwent 23 procedures: 3 dental care procedures under general anesthesia and 20 magnetic resonance imaging sessions under general anesthesia with a natural airway. At the time of anesthesia, the children were between 2–8 years old and had been on the KD for 2–24 months. While the mean duration of anesthesia was 56 minutes for magnetic resonance imaging, it was 146 minutes for dental therapy. Sevoflurane was used as an anesthetic agent during anesthesia induction and maintenance. Blood pH and glucose levels were monitored in patients who received general anesthesia for dental therapy. Blood glucose remained stable in all patients who underwent dental therapy, whereas blood pH decreased to 7.16 in one patient and IV bicarbonate was administered. There was no increase in seizure frequency from the baseline during the magnetic resonance imaging and dental therapy performed under general anesthesia. All patients were discharged home the same day, and only the dental care patient who had developed metabolic acidosis was hospitalized.

Conclusion

Non-surgical procedures requiring general anesthesia in children on KD are well tolerated, whereas blood pH and glucose analysis should be monitored in procedures longer than 2 hours

Keywords

Anesthesia; Acidosis; Ketogenic diet; Perioperative complications; Seizure

Introduction

In recent years, the ketogenic diet (KD) has been used quite frequently as an alternative treatment method for treatment-resistant epilepsy and some neurological diseases in pediatric patients (1). The high-fat, low-carbohydrate, and adequate protein intakes of these patients increase ketone production(2). The most common ratio frequently used in pediatric patients is 4:1 of fat (4 g),

carbohydrates (1 g), and protein. Although the anticonvulsant mechanism of diet-induced therapeutic ketonemia is not fully understood, it is known that the frequency of seizures decreases with KD. These patients may also need procedures that require anesthesia during their medical treatment. It is necessary to maintain a ketogenic state during procedures that require anesthesia and to ensure the continuity of the medical treatment of patients. They may face an increased risk of seizures, hypoglycemia, and metabolic acidosis due to prolonged fasting times, volume losses, surgical stress, and the use of intravenous fluids and medications that contain glucose. Therefore, pediatric anesthesiologists play an important role in the perioperative optimization of procedures requiring anesthesia in these patients.

In reports of small case series and case reports in the literature, it was stated that procedures requiring general anesthesia (GA) can be performed safely provided a ketogenic state is maintained(3–5). The aim of this study was to examine the perioperative risks in procedures that required GA in 4 pediatric patients actively on a ketogenic diet.

Methods

Between 2020–2022, 23 procedures performed under general anesthesia for 4 pediatric patients on KD were retrospectively analyzed. Demographic data of the patients, procedure and anesthesia type and duration, perioperative blood tests, KD history, hospital discharge times, and perioperative complications such as severe acidosis, symptomatic hypoglycemia, and increased seizure activity were recorded. The study complied with the Declaration of Helsinki on ethical principles for medical research involving human subjects. All parents or legal guardians provided written informed consent.

Results

Four male pediatric patients were evaluated retrospectively. Their ages ranged from 2 to 8 years, and they had a history of brain tumors and intractable epilepsy (generalized tonic–clonic seizures). All were taking 2 or more antiseizure medications. At the time of anesthesia, the children had been on KD for an average of 14 months (range 2–24 months). All patients were on a classical 4:1 KD ratio. To ensure the patients have maintained ketosis and stability on diet; ketone bodies were routinely monitored with home measuring devices by parents before the procedures. The demographic data of the patients, their KD history, and the antiseizure medications used are listed in **Table 1.**

Table 1: Characteristics of patients, ketogenic diet duration, and antiseizure medications

Patient no.	Age (year)	Weight (Kg)	Ketogenic diet duration	Antiseizure medications
1	8 y	22	24 months	Rufinamide, Clobazam, Phenobarbital, Ethosuximide
2	3 y	16	18 months	Vigabatrin, Clobazam, Levetiracetam
3	2 y	10	15 months	Vigabatrin, Clobazam
4	4 y	17	2 months	Phenobarbital, Topiramate, Valproic acid

A total of 23 procedures were performed, 20 under GA with natural airway and 3 under GA with endotracheal intubation (ETI). GA with ETI was administered for dental therapy, and GA with a natural airway was administered for magnetic resonance imaging (MRI). All patients were fasted for solid food 6 hours before the procedures and glucose-free clear fluids were allowed up to 2 hours before induction of anesthesia. All patients were instructed to take their usual antiseizure medications on

the morning of the procedure. The children were not premedicated for all procedures; anesthesia induction was performed in the parents' company to reduce their anxiety.

They resumed KD as soon as they woke after procedures.

In MRI patients, no blood analysis was performed before or after the procedure. However, symptomatic hypoglycemia and acidosis were not observed when evaluated clinically. Perioperative blood tests were examined for children who underwent dental therapy.

The blood glucose levels of 3 children who received GA for dental therapy were measured at induction, intraoperatively, and before awakening. The mean induction, intraoperative, and awakening blood glucose levels were 66 mg/dL, 68mg/dL, and 74 mg/dL, respectively.

Arterial blood pH levels were systematically monitored intraoperatively in these 3 patients due to the length of the procedure. They were measured as 7.16, 7.32, and 7.34, respectively.

MRI procedures under GA with a natural airway, induction, and maintenance of anesthesia were performed with sevoflurane via face mask while maintaining spontaneous breathing. Intravenous fluid and medications were not given throughout the procedure.

In patients who underwent dental therapy under GA with ETI, the induction and maintenance of anesthesia were also performed with sevoflurane.

Rocuronium and fentanyl were administered intravenously before intubation.

During the procedure, fentanyl was given when needed according to the hemodynamic response.

Glucose-free intravenous solutions (Ringer's lactate, normal saline) were used throughout the procedures. Propofol was not used as an anesthetic agent in any procedure. All patients (MRI and dental therapy) received standard monitoring and capnography and, intravenous access was provided at induction.

The total anesthesia time was between 40 min and 80 min for the 20 MRI procedures, with an average of 56 min. The average total anesthesia time for 3 dental therapy procedures was 146 min (120 min–200 min).

There was no increase in seizure frequency in the MRI and dental therapy procedures, as clinically evaluated before discharge home.

All patients were discharged uneventfully within the same day (when Modified Aldrete scores were 10), except one dental therapy patient who required a one-day hospitalization due to intraoperative severe metabolic acidosis.

After patients were discharged, their caregivers were contacted within 24 hours and asked whether there was increased seizure activity.

None of the patients had an increase in seizure activity after discharge home.

Procedure information, type and duration of anesthesia, drugs used, perioperative complications, blood pH and glucose levels, and hospital discharge times are listed in tables 2 and 3.

Table 2: MRI procedures under general anesthesia. **MAT**: Mean anesthesia time, **MRI**: magnetic resonance imaging

Patient no.	Procedure type	MAT (min)	Medications administered	Mean Discharge time (min)	Number of MRIs performed	Complications
1	MRI	59	Sevoflurane	113	10	none
2	MRI	56	Sevoflurane	93	8	none
4	MRI	42	Sevoflurane	95	2	none

Table 3: Dental therapy procedures under general anesthesia. **AT**: anesthesia time, **RL**: Ringer's lactate, **NS**: normal saline, **DT**: discharge time

Patient no.	Procedure type	AT (min)	Medications administered	DT (hour)	Intraoperative Blood PH	Complications	Induction glucose (mg/dL)	Awekening Glucose (mg/dL)
1	Dental therapy	200	Sevoflurane Rocur 0.6 mg/kg, Fentanyl 3 µg/kg Ondansetron 0.1mg/kg Sugammadex 4mg/kg RL 10 ml/kg/h	24 h	7.16	Metabolic acidosis	67	78
2	Dental therapy	120	Sevoflurane Rocur 0.6 mg/kg, Fentanyl 3 µg/kg Ondansetron 0.1mg/kg Sugammadex 4 mg/kg RL 8 ml/kg/h	8 h	7.32	None	62	75
3	Dental therapy	120	Sevoflurane Rocur 0.6 mg/kg, Fentanyl 3 µg/kg Ondansetron 0.1mg/kg Sugammadex 4 mg/kg RL 5 ml/kg/h NS 5ml/kg/h	6 h	7.34	None	69	70

Intraoperative acidosis developed in 1 of 3 children who underwent dental therapy. This 8-year-old patient (Patient 1) with a history of craniotomy for the resection of a brain tumor had resistant epilepsy that was well controlled with four antiseizure medications and KD therapy. He received GA for 3 hours and 20 minutes for dental therapy. Blood pH and glucose were checked at the 2nd hour of the procedure. Blood glucose remained stable compared to the-induction value. However, the blood pH decreased to 7.16, and metabolic acidosis had developed. He was administered intravenous sodium bicarbonate 8.4% 30 ml/Eq. The patient, whose acidosis improved (pH:7.38), was extubated at the end of the procedure. After observation in the postoperative care unit for 1 hour, he was followed up in the hospital for one day. The patient, who had an uneventful night, was discharged without increased seizure activity or hypoglycemia.

Discussion

In this retrospective review of 23 procedures performed on 4 pediatric patients actively on KD, it was observed that MRI procedures under GA with sevoflurane and natural airway were well tolerated. These 4 children, who were followed up for brain tumors and epilepsy, often received recurrent anesthesia for MRI, which is essential during their routine follow-up. In 20 GA for MRI, there was no increased seizure activity. However, intraoperative acidosis was observed in one patient who received GA for dental therapy, which was corrected with bicarbonate replacement. No serious life-threatening complications were reported in previous reviews of patients with KD.(4,6) Almost all reported cases consisted of surgical procedures. In Soysal et al.'s review of 24 patients and 33 procedures, deep acidosis and the associated increase in seizure activity were observed in three patients(3). In Valencia et al., metabolic acidosis requiring treatment was

observed in 3 patients, while mild acidosis not requiring treatment was frequently observed in other case reports(4,6).

Although mild baseline metabolic acidosis is frequently encountered in these patients, deeper metabolic acidosis may be observed depending on surgical stress, prolonged fasting periods, volume losses, and the type of intraoperative fluids and medications. Although there is no clear recommendation about intravenous fluids that can be used in these patients, Ringer's lactate (RL) and normal saline (NS) are frequently used. Some authors reported that although RL does not contain glucose, it is relatively contraindicated because of the possibility of disrupting the ketogenic state through gluconeogenesis (3). Consequently, acetate-containing solutions (e.g., Plasmalyte) may be a better option, as lactate can be transformed into glucose. Conversely, when NS is administered in high amounts, it can cause metabolic acidosis due to chloride load. In our case-study patient who developed metabolic acidosis, 10 ml kg/h RL was used. In cases longer than 2 hours, acetate-containing solutions or the alternate use of RL and NS may provide more appropriate fluid management in these patients.

In addition, nephrolithiasis may be seen in these patients due to chronic metabolic acidosis. Many children with KD are advised to use oral citrate (e.g., CitraK or PolycitraK) empirically to prevent kidney stones and acidosis by alkalinizing the urine(7). Patients using oral citrate may have less risk of intraoperative severe acidosis. All the children in our case series used oral citrate. Since mild baseline asymptomatic acidosis is quite common in patients undergoing KD therapy, measuring serum pH during induction may be useful for intraoperative follow-up in procedures requiring long-term anesthesia. However, there is no clear recommendation in the literature about the cut-off value of acidosis that requires IV bicarbonate in the intraoperative period.

One major concern in the anesthesia management of these patients is hypoglycemia. Prolonged preoperative fasting periods should be avoided. In patients with active KD, serum glucose levels may be low (50–80 mg/dL)(8). To avoid deteriorating ketosis, it is not recommended to intervene unless the blood sugar falls below 40 mg/dL if it is asymptomatic(9). In cases reported by authors such as Valencia, Soysal, Mcneely, and Hinton, hypoglycemia was not observed in any patient (3,4,6,10). In our patients, symptoms of hypoglycemia were not observed in any of the 23 procedures, although blood glucose monitoring was performed only in three patients who received GA for dental therapy. In MR cases, perioperative pH and glucose monitoring were not performed because the procedure time was short, patients were not exposed to surgical stress, and anesthesia was administered without ETI by the natural airway without the need for multiple drug administration. In cases where GA with ETI is not performed and the procedure duration is less than 2 hours, the symptomatic follow-up of patients regarding hypoglycemia may be appropriate.

Another important issue during the anesthesia management of these patients is oral and parenteral medications. Antiseizure medications should never be stopped in the morning of any procedure. Skipping or late taking antiseizure medications may cause patients to have seizures. Many oral and IV medications used in anesthesia may contain glucose and increase the risk of seizures with the loss of ketosis. For example, oral midazolam solutions used in the premedication of pediatric patients contain high amounts of glucose(11). Since they do not contain glucose, premedication can be provided by the intranasal administration of dexmedetomidine(12). In cases with the unknown carbohydrate content of any medication administered to patients with KD, the package insert should be examined. Avoiding polypharmacy will also prevent accidental carbohydrate entry. In our case, anesthesia induction and maintenance were performed with sevoflurane. Parents accompanied children during induction to reduce children's anxiety. Propofol was not used in any of our cases. Despite its triglyceride and low carbohydrate content (glycerol: 22.5 mg/mL), a high dose (> 4 mg/kg/hour) and long-term infusion (> 48 hours) of

propofol is not recommended due to the risk of metabolic acidosis and propofol infusion syndrome(9,13). In patients on KD, 90% of caloric needs are obtained from fat (long-chain triglycerides). One of the most common adverse effects of this diet is hyperlipidemia(14). The prolonged infusion of propofol may also cause acute pancreatitis by aggravating pre-existing hyperlipidemia. However, in most reported cases, propofol was used safely at single doses of 4 mg/kg and below for anesthesia induction in patients with KD(3,4).

The literature has examined the management and progress of patients with KD in surgical procedures that generally require GA with ETI. Our case series consists mostly of non-surgical procedures. We did not clinically observe any perioperative complications during 20 MRIs. The mean duration of anesthesia for MRI cases was 56 min. It seems that MRI procedures under GA with sevoflurane and natural airway in children with KD, especially under 2 hours, can be performed with close clinical observation and low perioperative risk.

The present study has some limitations. Since MRI procedures are considered non-invasive procedures, blood glucose, and blood pH measurements were not performed in MRI patients. In addition, the small number of patients and the retrospective design of the study are other limitations.

Conclusion

Anesthesia seems to be well tolerated in children undergoing KD therapy. The avoidance of high-carbohydrate medications and fluids, prolonged fasting times, dehydration, and maintenance of therapeutic ketosis will reduce perioperative complications in these patients. It is important to monitor serum pH and glucose, at least during induction and awakening. They should be checked hourly in procedures lasting longer than 2 hours.

Abbreviations

KD: Ketogenic diet, GA: general anesthesia, MRI: magnetic resonance imaging, RL: Ringer's lactate, NS: normal saline

Declarations

Authors' contributions SAY, ZSUO designed the study, and SAY drafted and modified the manuscript. All authors read and approved the final manuscript. The manuscript has not been submitted to more than one journal for simultaneous consideration. This manuscript has not been published previously.

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Availability of data and materials The datasets for the current study are available from the corresponding author on reasonable request.

Ethical approval Ethical approval was obtained from the Regional Ethical Committee of Acibadem MAA University (protocol no: ATADEK-2022-12/37)

Consent to participate The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients.

Competing interests The authors declare that they have no competing interests.

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