Tolerance and response to ketogenic therapy in neonates and infants younger than 4 months. Case series in a hospital center in Medellín, Colombia

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Introduction. Ketogenic therapy (KT) studies have focused in children older than 2 years and adults. Recently its efficacy in infants has been reported, but there are few studies in this age group.

Patients and methods. We report a case series of nine newborn and children younger than 4 months of age with refractory epilepsy treated with KT. We retrospectively reviewed charts of children treated at our center between 2015-2021.

Results. Data was collected on seven patients. Six patients began having seizures on day one of life, one had seizures starting on day 45. Different epilepsy etiologies were found. KT was started as soon as 9 days of life. The average age at which ketogenic therapy was started was 24 days of life. Initially, the diet was started at 1:1 or 2:1 ratio, and was progressed to a 4:1 ratio. After one month of KT 5/7 patients experienced a significant reduction in seizure frequency (>50%) and 2/7 had complete seizure control. At six months, 4/7 patients achieve complete seizure freedom and 1/7 had >50% seizure reduction. Two patients were lost to follow-up. None of our patients reported gastrointestinal side effects that required diet adjustments. One patient had mild and one mild hypertriglyceridemia.

Conclusion. Even though evidence about KT in young children are starting to emerge, our experience shows it can be successful in controlling seizure burden without considerable adverse effects. There is great research potential regarding KT in young children.

Key words. Epilepsy. Ketogenic diet. Ketogenic therapy. Neonatal epilepsy. Neonatal seizures. Refractory epilepsy.

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Introduction

Neonatal seizures are a manifestation of significant brain dysfunction and often carry an unfavorable neurological prognosis [1]. In recent years there have been studies that have tried to find novel and efficacious therapeutic options with acceptable adverse event profile in this age group. Until now the options are still very limited with an unsatisfactory efficacy [2-4].

Ketogenic therapy (KT) has been used for several years as a non-pharmacological therapy for epilepsy, and its effectiveness in the management of refractory epilepsy has been demonstrated in several studies and systematic reviews [5,6]. Those reports focused on children older than 2 years and adults. In recent years different authors have reported good results in childhood epilepsy [7-10]; but data on young infants and neonates are missing. Concern exists regarding special nutritional requirements and worries of theoretical possibility of greater adverse effects in this age group. Suitable and ethical methodological designs are also difficult in these age groups.

In 2020, Lyons et al [11] published a systematic review on the use of KT in infants younger than 2 years of age. A total of 33 articles with 534 infants were included. Sample size and methodological heterogeneity were evident and only two of the studies included a few patients under 28 days. They found that 59% of infants had more than 50% seizure reduction and 33% achieved complete seizure control with overall few adverse effects. In the same year, Falsaperla et al published a literature review [12]; including 50 articles on KT emphasizing on children younger than 2 years of age. They concluded that KT and its variants are safe and useful in the management of refractory epilepsy in patients between 0-23 months of age. Both articles advise on the need of high quality methodological studies for this age group.

There are few studies and no clinical practice guidelines of KT that focus on neonates. An expert consensus was published in 2016 providing recommendations regarding initiation and follow-up of KT in infants [13]. As far as it is known, there are no local studies that report the usefulness of this therapeutic option in the first months of life. Therefore, we wanted to report the experience of the Clínica Universitaria Bolivariana in the city of Medellín, Colombia, with the use of the KT in neonates and infants under 4 months of age.

Patients and methods

We conducted a descriptive, case series study. The co-investigators retrospectively reviewed the medical records of neonatal and infant patients younger than 4 months with refractory epilepsy who received KT between 2015 and 2021 at the institution. The data was entered in an Excel form designed with validation cells to reduce typing errors. The following variables were registered: perinatal history: gestational age at birth, weight, length, head circumference, Apgar score, electrical and clinical features of seizures before the onset of KT, etiology of epilepsy, nutritional status, type of formula, ratio used at the beginning and the end impact on the number of seizures, electroencephalogram after the onset of KT; and adverse effects: hypoglycemia, diarrhea, constipation, vomiting, metabolic acidosis, dyslipidemia, abnormalities in hepatic tests, and weight, and breastfeeding changes.

The imaging, labs and electroencephalogram were carried out as part from the usual medical procedures of the pediatric neurology service for the approaching each patient's diagnosis. All underwent electroencephalogram, brain magnetic resonance imaging, and basic biochemical studies. Those patients which did not have a clear etiological cause to their epilepsy were screened for inborn errors metabolism (ammonium, lactate, quantitative amino acids in blood and cerebrospinal fluid, quantitative organic acids in urine, and acylcarnitine profile). In Colombia, newborn screening for inborn errors of metabolism is not performed routinely. Biochemical tests are costly and results take a great amount of time to get back. Patients in which metabolic or genetic epilepsy was suspected had this analysis performed. In patients in which the cause of epilepsy was clear (structural, hypoxic ischemic), we did not wait for these results as it would delay therapy and possibly worsen prognosis. Failure of two antiseizure medications were considered refractory seizures (refractory epilepsy). In these cases, the diet was indicated by a medical staff including the institution's pediatric neurologist, neonatologist and nutritionist, considering there were no contraindications. Parental informed consent was obtained before starting the KT. The nutrition team verified data concerning weight, length, head circumference, breastfeeding, and nutritional requirements. KT was started with a powdered formula with high-fat and low-carbohydrate content; initially the diet was calculated with a 1:1 or 2:1 ratio, and after one week it was progressed to a 4:1 ratio. Commercial formula Ketocal® was used in all but one infant. Patient 3 received commercial formula Ketovolve®. Choice of formula was based on which was more readily available at the time of initiation. Patient 1, which had a metabolic etiology of epilepsy (glycine encephalopathy) received regular ketogenic formula, with protein restriction 2-2.5 g/kg/day.

Statistical analysis was descriptive. Excel 2010 was the statistical program used. Qualitative variables were expressed in relative and absolute frequencies. Quantitative ones were expressed as mean with their standard deviation if they had a normal distribution; otherwise, they were expressed as median and interquartile range. The study was approved by the Clínica Universitaria Bolivariana Ethics Committee.

Results

Seven patients were enrolled; all full-term newborns with adequate birth weight. All started neonatal seizures on the first day of life, except one that started at 45 days of birth. All patients had frequent seizures occurring daily or several times a week. Seizure etiology was heterogenous. The demographic and clinical characteristics are described in table.

The average age of initiation of the KT was 24 days of life with a range between 9 days and 4 months. Six of the patients were admitted at the time of initiation and one of them was started as an outpatient. Of the seven subjects, four were breastfeeding at the beginning of the KT, which was continued with expressed breast milk, as long as the therapy had a 1:1 or 2:1 ketogenic ratio. Breastfeeding was withdrawn when approaching to the 4:1 ratio to maintain required carbohydrate to fat ratio. The diet was started with a 1:1 ratio in six patients and 2:1 in one patient, and it was increased to 4:1 ratio in all patients except one, who reached a 3:1 ratio.

All patients were enrolled to the pediatric KT program. Follow-up appointments were planned

Table. Clinical and demographic characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Birth weight (grams)	3,400	3,700	3,250	2,480	4,050	2,985	3,505
Age at first seizure	Day 1	Day 45	Day 1	Day 1	Day 1	Day 1	Day 1
Type of seizures	Clinical-electrical/ clonic, myoclonic, tonic	Clinical-electrical/ epileptic spasms	Clinical-electrical/ clonic, tonic	Clinical-electrical/ tonic	Clinical-electrical/ clonic	Clinical-electrical/ tonic, clonic	Predominant electric seizures/ tonic, clonic, spasms.
Seizure frequency before KT	3-4 times a week	Daily	Daily	Daily	Daily	Daily	Daily
Epilepsy etiology	Metabolic (glycine encephalopathy)	Undefined	Genetic (KCNQ2 mutation)	Unknown	Structural (multicystic encephalomalacia secondary to perinatal asphyxia)	Structural (multicystic encephalomalacia secondary to perinatal asphyxia)	Structural (extensive pachygyria)
Antiseizure medication pre-diet	FNB, LVT	FNB, LVT, VGB, OXC	FNB, LVT, CBZ, VGB, VA, TPM	FNB, LVT, TPM	FNB, LVT, TPM	FNB, LVT, VGB, CBZ	FNB, LVT
Age at start of KT (days)	40	120	40	24	17	24	9
Initial/final ketogenic ratio	1:1/4:1	1:1/4:1	1:1/3:1	1:1/4:1	1:1/4:1	1:1/4:1	2:1/4:1
Administration route	Nasogastric tube	Oral	Oral	Oral	Nasogastric tube	Nasogastric tube	Nasogastric tube
Adverse effects	None	Mild hypertriglyceridemia (resolved completely)	Hypoglycemia	None	None	None	None
Seizure control after ketogenic diet							
At one week	>50% (encephalopathy also improved)	>50%	100%	>50% (encephalopathy also improved)	>50%	>50%	>50%
At one month	>50%	100%	100%	>50%	>50%	>50%	>50%
At six months	>50%	100%	100%	100%	Lost to follow-up, socioeconomic issues	Lost to follow-up, therapy abandonment	100%

CBZ: carbamazepine; FNB: phenobarbital; LVT: levetiracetam; OXC: oxcarbazepine; VGB: vigabatrin; TPM: topiramate.VA: valproic acid.

monthly. At each visit seizure control, tolerance, adherence, labs, and nutritional status were assessed. Of the seven patients, two did not continue with KT: one of them (patient 6) discontinued it by her parents' decision at 2 months of life, without reporting adverse effects; additionally, in patient 5, it was not possible to carry out adequate follow-up after 2 months of life due administrative insurance issues.

One month after KT onset, 2/7 achieved complete seizure remission and 5/7 had more than >50% of seizure reduction. Data were available for five patients at six months of therapy. Of these, four patients had complete seizure improvement, and one

patient had partial improvement, with a reduction of more than >50% of seizures. Additionally, in two subjects (patients 1 and 4) it was also possible to identify an improvement in awareness and improvement in encephalopathy. Seizure follow-up was recorded based on parent observation and clinical and electroencephalogram monitoring while in the hospital. All patients experienced improvement in their electroencephalogram tracings obtained while in the neonatal intensive care unit as well the ones obtained as outpatients.

Regarding adverse effects, none reported gastrointestinal intolerance that prompted diet suspension or adjustments. One patient had mild hypoglycemic episodes associated with vomiting at the beginning of the diet, which did not recur (patient 3). Lipid profile data were obtained at follow-up in 4/7 patients, only one reported mild hypertriglyceridemia (patient 2).

Discussion

In this case series we report the experience with the introduction of KT in seven patients, mostly neonates (six patients). Seizures breakthrough started as early as the first day of life, and quickly met refractory seizure criteria. KT was started during the first 6 weeks of life in 6/7 patients, all having a good response, with only clinical mild adverse effects in two patients. Lab follow-up demonstrated hypertriglyceridemia or hypoglycemia in two patients. No patients required reduction or withdrawal of KT.

The etiology of epilepsy in this group of subjects was diverse, which supports the KT usefulness for the management of refractory epilepsy, regardless of its cause. Etiology work-up and antiseizure medication failure prompted the decision to start KT aiming seizure control and developmental success. Complete seizure control was achieved in four patients and two improved their awareness state.

Recently, Dressler et al [8] described 20 studies of KT in children, including patients under one year of age, but they did not include neonates. Case reports and cohort studies were included; seizure reduction >50% was achieved in 48-80% of patients. Seizure freedom was achieved in 14-54%. Few adverse effects were described. The study doesn't make a thorough analysis of children under 12 months of age.

Thompson et al [9] reported the use of KT in four young infants in a neonatal intensive care unit, being the minimum age for starting the diet at 6 weeks of age. They subjective improvement of the seizures in three of them and a low profile of adverse effects in all. Le Pichon et al [14], in a cohort study that included nine infants with refractory epilepsy, aged between 1 and 13 months, reported the experience with the use of KT and breast milk. They found that four of them had a >50% decrease in seizures in the first visit, three became seizure-free, and one did not have a change in seizure frequency. The diet was generally well tolerated, although one child required hospitalization for acidosis and dehydration. This data are similar to our findings, regarding seizure reduction, diet tolerance and low frequency of side effects.

We started the diet in the first month of life in four of the subjects, even as early as 9 days of life in one of them, with a significant improvement in seizure reduction in all patients. In the literature review, we did not find any study starting KT during the neonatal period. We achieved a seizure control that exceeded 50% in an early and safe way. The two cases of treatment withdrawal of KT were not related to the diet itself but parental decision and insurance difficulties. In addition, the administration of the diet was easy through commercial milk formulas and with an increase in the relationship according to metabolic and gastrointestinal tolerance.

We also highlight that in two patients it was possible to identify a significant improvement in the alertness state. This is important since the positive effects of KT have been shown to go beyond seizure control [15,16]. This may be explained through the multiple mechanisms of action that have been demonstrated for this therapy, apart from the production of ketosis [17].

Side effects were rare. Mild hypoglycemia and hypertriglyceridemia occurred, in one patient each. Those side effects were temporary and did not require discontinuation of therapy. Hypoglycemia is usually more frequent when starting the KT. Glucose levels should be measured periodically at the beginning, especially in young and malnourished children [13,18]. Similarly, dyslipidemia occurs in the first weeks of therapy and usually improves in the following months [19,20].

Limitations

We recognize several limitations, the main one being the small number of patients and the retrospective nature of the study, as well as the loss of follow-up of two of the subjects.

Due to administrative issues of the Colombian regulatory healthcare system, KT is not timely and widely available. This creates obstacles for its adherence in the first year of life and may discourage its use in patients that could benefit from it. Larger published experiences are needed to set a strong background for its universal approval.

Conclusion

In this case series, a successful experience was shown with the use of the KT in neonates and young infants. Although it is clear that this is only an initial report of a small number of patients, it is very valuable to be able to show that a good epileptic seizure control can be achieved quickly and safely, without serious side effects. We encourage research of KT in neonates and young infants in larger, prospective studies considering long-term follow-up of seizure control, neurodevelopment, lab, electroencephalogram and neuroimaging data. Moreover, publishing this data could promote its use in younger ages worldwide.

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Descripción de la tolerancia y respuesta a la terapia cetógena en neonatos y lactantes menores de 4 meses. Serie de casos en un centro hospitalario de Medellín, Colombia

Introducción. Los estudios para terapia cetógena (TC) se han concentrado en niños mayores de 2 años y adultos. Su eficacia en lactantes se ha descrito, pero hay pocos estudios en este grupo de edad.

Pacientes y métodos. Se describe una serie de casos de nueve neonatos y lactantes menores de 4 meses de edad con epilepsia refractaria que recibieron tratamiento con TC. Se evaluaron retrospectivamente los registros clínicos de niños tratados entre 2015 y 2021.

Resultados. Se recolectaron datos de siete pacientes. Seis pacientes iniciaron con crisis epilépticas el primer día de vida, y uno, el día 45. La etiología de la epilepsia fue variada (metabólica, genética y estructural). La TC se inició tan temprano como a los 9 días de vida. La edad promedio de inicio fue los 24 días de vida. Se inició con una tasa cetógena de 1:1 o 1:2, y se progresó posteriormente a 4:1. Después de un mes de TC, 5/7 pacientes presentaron una reducción significativa en la

frecuencia de las crisis (>50%) y 2/7 experimentaron un control completo. A los seis meses, 4/7 pacientes lograron un control completo y 1/7 un control >50%. Dos pacientes se perdieron en el seguimiento. No se notificaron efectos gastrointestinales que obligaran al ajuste o la suspensión de la dieta. Se notificaron hipoglucemia e hipertrigliceridemia.

Conclusión. A pesar de que la evidencia en la TC en lactantes y neonatos apenas está empezando a aparecer, nuestra experiencia muestra que puede ser una buena opción terapéutica para el control de las crisis epilépticas, sin efectos adversos importantes. Existe un gran potencial de investigación en el área de la TC en lactantes y neonatos.

Palabras clave. Crisis neonatales. Dieta cetógena. Epilepsia. Epilepsia neonatal. Epilepsia refractaria. Terapia cetógena.