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Vitamins and Minerals Vs Ketogenic Diet in Management of Refractory Epilepsy?

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KEYWORDS

Epilepsy, Refractory Epilepsy, Ketogenic Diet, Vitamins, Steroids

ABSTRACT:

Introduction: Epilepsy, a chronic disorder with recurrent seizures, is challenging to manage, especially in cases resistant to standard antiepileptic drugs (AEDs).

Aim of the study: We aimed to determine which is better in management of refractory epilepsy in pediatrics (mixed steroid and ketogenic diet or multivitamins)

Methods: It is a randomized, single-blinded study at Assiut University Children Hospital, Egypt (October 2020–October 2021), 70 patients aged 1-17 with refractory epilepsy were assigned to two treatment groups: Group 1 received multivitamins (zinc, copper, magnesium, vitamins A, C, D, selenium, calcium), and Group 2 received corticosteroids followed by a ketogenic diet. Both groups continued their standard AED regimen. Changes in seizure frequency, metabolic parameters, radiological findings, and overall improvement were assessed.

Results: No significant differences in demographic and neurological assessments, laboratory and radiological findings were noted. Generalized seizures were more common. The vitamin group had the highest overall improvement, though convulsion frequency changes but had insignificant difference from another group.

Conclusion: Both treatments showed limited impact on convulsion frequency

1. Introduction

Epilepsy, a chronic neurological disorder marked by recurrent seizures, presents significant management challenges, especially in cases resistant to standard treatments. Despite advancements in antiepileptic drugs (AEDs), some patients continue to experience uncontrollable seizures, necessitating alternative or adjunctive strategies. Dietary interventions and nutritional supplements have emerged as potential adjuncts to conventional therapies **[1].**

The ketogenic diet, a high-fat, moderate-protein, and very low-carbohydrate regimen, has gained attention for its potential benefits in managing refractory epilepsy. Developed in the 1920s, this diet induces ketosis, shifting the body's energy source from glucose to ketone bodies derived from fat metabolism **[2].**

In addition to dietary approaches, vitamins and nutritional supplements have been investigated for their role in epilepsy management. Vitamins such as B6, B12, and D have shown potential in modulating seizure activity and improving neurological function. Recent studies suggest that deficiencies or imbalances in these nutrients may affect seizure susceptibility, and supplementation might support the management of refractory epilepsy **[3].**

Corticosteroids, including prednisone and dexamethasone, have also been explored as therapeutic

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options. These anti-inflammatory agents can modulate immune responses and neuronal excitability, and have shown promise in conditions where inflammation or autoimmune mechanisms contribute to seizure activity, such as autoimmune epilepsy and epileptic encephalopathies**[4].**

2. Patients and methods

2.1. Study design and setting.

This study was a randomized, single-blinded trial conducted at the Pediatric Neurology Unit of Assuit University Children Hospital (AUCH) in Egypt, spanning from October 2020 to October 2021.

2.2. Selection criteria

The study included patients aged between 1 and 17 years, irrespective of sex, who were diagnosed with epilepsy and had been on a regimen of two well-tolerated antiepileptic drugs, according to ILAE guidelines (2009)**[5],** but had shown no improvement over a duration of six months. All types of epilepsy were considered. Exclusion criteria encompassed infants under 1 year, patients on monotherapy or those with poor medication adherence, as well as individuals with conditions that mimic epilepsy, such as cardiogenic events, vasovagal syncope, parasomnias, movement disorders, or psychogenic non-epileptic seizures.

2.3. Participants

Each participant underwent a comprehensive evaluation, starting with a detailed history that included sex, age at the onset of epilepsy, family history (including consanguinity and similar conditions in siblings), and information on the types and duration of antiepileptic medications administered. Clinical examination was conducted to identify any neurocutaneous syndromes, characterized by specific facial features or skin lesions, and included a thorough neurological and systemic assessment.

Investigations involved a range of tests, including electroencephalogram (EEG), renal and liver function tests, serum electrolytes and glucose levels, and brain imaging via computed tomography (CT) or magnetic resonance imaging (MRI). Additionally, a metabolic workup was performed, including arterial blood gas analysis, serum ammonia, lactate levels, and tandem mass screening. Genetic testing, including karyotyping and gene sequencing, was also carried out. Fundus examination was performed if needed, and cerebrospinal fluid (CSF) culture and analysis were conducted if indicated.

The study comprised 70 patients with refractory epilepsy, who were randomly assigned to one of two treatment groups.

The first group received a supplement of multivitamins and trace elements, including zinc (50-500 µg/kg/day, with a maximum of 5-6.5 mg/day), copper (20 µg/kg/day), magnesium (80-120 mg/day), vitamin A (3,000 IU/day), vitamin C (75 mg/day), selenium (2-3 µg/kg/day, with a maximum of 60-100 µg/day), vitamin D (1,000 IU/day), and calcium (40-80 mg/kg/day).

The second group received corticosteroid therapy followed by a ketogenic diet. The corticosteroid regimen consisted of a pulse dose of 30 mg/kg/day for 5 days (with a maximum of 1 g/day), administered monthly for 6 months. The ketogenic diet was initiated with a 3:1 or 4:1 fat-to-combined carbohydrate and protein ratio, with a gradual increase in fat content over 3 days. For children under 2 years, the diet consisted of Ketocal milk formula, while children over 2 years were placed on a low-carbohydrate diet adjusted according to the family's socioeconomic status, food availability, and maternal education. The diet included various proteins (meals, eggs, seafood, unsweetened dairy products, poultry, legumes, beans, chickpeas, peas, seeds, nuts, lean cuts of beef and pork) and fats (coconut oil, vegetable oil, sesame oil, nuts, salmon, tuna, olive oil).

Patients were followed up to monitor seizure frequency, antiepileptic drug adherence, and dietary compliance. Follow-up involved regular visits, 24-hour dietary recalls, and phone contact (daily during the first month and weekly thereafter). Additionally, investigations included measuring urine ketones and blood glucose levels

3. Ethical approval and consent of participation

The Ethics Review Board of the Faculty of Medicine at Assiut University gave their consent to the study protocol before its implementation. Informed written consent was collected from all participants in compliance with the Helsinki Declaration **(Clinicaltrails.gov NCT 04542629).**

4. Statistical analysis

Using SPSS software, version 25, which was developed by SPSS Inc., which is situated inChicago, Illinois, United States of America, the data analysis was carried out. The Chi-square test was utilized to compare the

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categorical variables that were present in both groups. On the other hand, the Student T-test was utilized to compare the continuous variables. To do statistical analysis, we used the Shapiro-Wilkes test to determine whether the data were normally distributed.. If a p-value is less than 0.05, then it is regarded to be statistically significant. Using SPSS software, version 25, which was developed by SPSS Inc., which is situated in Chicago, Illinois, United States of America, the data analysis was carried out.

The Chi-square test was utilized to compare the categorical variables that were present in both groups. On the other hand, the Student T-test was utilized to compare the continuous variables. To do statistical analysis, we used the Shapiro-Wilkes test to determine whether the data were normally distributed. If the p-value is less than 0.05, then it is regarded to be significant.

5. Results

Comparison of Demographic data and neurological assessment between the two studied groups as shown in table (1) and table (2)

There were insignificant differences between both groups in all items

Regards The types of convulsions, generalized fits was higher than focal types. Few patients showed myoclonic or absence seizure as shown in figure (1)

Regarding the comparison of the investigations done for patients as shown in table (3)

There were some increases in renal function tests and lipogram,As regards metabolic diseases; fatty acid oxidation defect and organic academia were also detected in some cases with insignificant difference between both groups

6. Regarding the comparison of radiological findings between the two studied groups as shown in table (4)

CT and MRI brain studies are abnormal in more than 20%, 31% of patients respectively with no significant difference in both groups where they show variety of findings as (atrophy, Dandy walker, demyelination, encephalitis, encephalomalacia, hydrocephalus, limbic encephalitis, Rasmussen encephalitis, tuberous sclerosis, polymicrogyria, hypoxic ischemic encephalopathy).

Regarding the comparison of the frequency of convulsion as shown in table (5)

After enrollment to the study, frequency of fits in the follow up was slightly lowered in vitamin group with insignificant p value, with no change in the other group

Discussion

The lack of significant differences in demographic and neurological assessments between the two groups is consistent with findings from **Omrani(2019)**who reported similar baseline characteristics in their comparative study of epilepsy treatments, first group was received vitamins and the other received placebo. this suggests that both treatment groups were comparable at baseline, allowing for a fair evaluation of the interventions **[6].**

Our study found a predominance of generalized fits over focal seizures, with few cases of myoclonic or absence seizures. This in contrast to **Beghi (2020)** study that show that most common type of epilepsy is focal type in both children and adults, but in most low /middle income countries the most reported type is generalized tonic clonic type. This is a reflection of under ascertainment of the other seizure types as a lack of recognition and diagnostic tools where generalized seizure is more serious **[7].**

Our study observed some cases with raised lipid levels and renal function markers. Depending on a previous study found that Vitamin B6 supplementation led to significant improvements in lipid profiles among epilepsy patients, their study supports the idea that vitamins can modulate lipid metabolism, potentially influencing treatment outcomes and side effects related to lipid dysregulation so it is advised to follow up those results after treatment [**8].**

ABG was done for all patients and show acidosis in8.5 % and 5.7% in patients who started mixed therapy and vitamins therapy respectively and Extended metabolic screening done for all patients. In this study, number of patients diagnosed with metabolic disorder is few (Metabolic diseases are relatively uncommon causes for pediatric seizures; however, they should always be considered when evaluating children presenting with seizures. Various metabolic disorders can cause seizures including amino acids metabolic disorders, disorders of energy metabolism, cofactor-related metabolic disorders, purine and pyrimidine

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metabolic disorders, peroxisomal and lysosomal diseases, and congenital disorders of glycosylation **[9].**

Metabolic diseases can cause seizures by different mechanisms. Seizures can occur due to the accumulation of toxic metabolites such as ammonia. Hyperammonemia occurs in several metabolic diseases such as disorders of the urea cycle and organic acidemias. Ammonia accumulation is neurotoxic as it results in increased glutamine synthesis causing swelling of astrocytes and brain edema. Some metabolic disorders can disturb neurotransmission. Glycine is an NMDA (N-methyl D-aspartate) glutamate receptors agonist. Glycine accumulation in glycine encephalopathy results in overstimulation of the excitatory NMDA receptors causing seizures **[10].**Although inborn error of metabolism (IEM) is considered as an infrequent cause of epilepsy it is estimated that there are more than 200 IEM encompassing seizures or epilepsy, however, the true number is unknown **[11].**

In this study, CT Brain and MRI Brain studies (Tables 4) are abnormal in more than 20%, 31% of patients respectively where they show variety of findings as (atrophy, Dandy walker, demyelination, encephalitis, encephalomalacia, hydrocephalus, limbic encephalitis, Rasmussen encephalitis, tuberous sclerosis, polymicrogyria, hypoxic ischemic encephalopathy). This structural abnormality is significantly related to refractioness of epilepsy. In agreement with the present study, ***Mishra (2019)*** states that localisation of the epileptogenic zone and structural cerebral abnormalities play important role in refractoriness. The temporal lobe is the most epileptogenic area because it is the most common of the focal epilepsy syndrome. Cortex is another area with low seizure thresholds **[12].**

The slight reduction in convulsion frequency in the vitamin group, though statistically insignificant, contrasts with findings from another author who reported more critically, children with epilepsy receiving VitD supplementation achieved good seizure control in his study **[13].** This discrepancy may be due to differences in treatment duration or dosages.

No significant change in convulsion frequency in the mixed steroid and ketogenic diet group, this in association with A study by Kwan et al. (2004) investigated the efficacy of combined steroid and ketogenic diet therapies in epilepsy patients and reported similar results regarding convulsion frequency. They found that while the ketogenic diet was effective in reducing seizure frequency in some patients, the combination with steroid therapy did not significantly alter convulsion frequency compared to control groups **[14].**

Conclusion

This study aimed to compare the effects of two different treatment protocols; vitamin supplementation versus a mixed steroid and ketogenic diet on various aspects of patient health in individuals with refractory epilepsy. Overall, the study highlights that there is lack of significant changes in convulsion frequency in both groups

7. Statements and Declarations

- **Acknowledgments:** Not applicable
- **Data availability:** The data used in this research are available from the senior author upon any reasonable request.
- **Compliance with Ethical Standards**
- **Conflict of interest:** The authors have no relevant financial or non-financial interests to disclose.
- **Funding:** No funds, grants, or other support was received.
- **Ethical approval**:The study protocol received approval from the Ethics Review Board of the Faculty of Medicine, Assiut University. Informed written consent was collected from all participants by the declaration of Helsinki.*Clinicaltrails.gov*. **NCT 04542629**
- **Author contributions:** All authors contributed to the study's conception and design.Conceptualization: [Noha ElGyar , Nancy Alaa Elgalaly], Methodology: [Eman Fathala Gad and Osama Mahmoud EL Asheer], Formal analysis and investigation: [Emad El-Deen Mahmoud Hammad EL Daly , Duaa Mohammad Raafat], Writing - original draft preparation: [Noha ElGyar , Nancy Alaa Elgalaly], Writing - review and editing: [Noha ElGyar , Nancy Alaa Elgalaly], Supervision: [Emad El-Deen Mahmoud Hammad EL Daly , Duaa Mohammad Raafat]. All authors read and approved the final manuscript.

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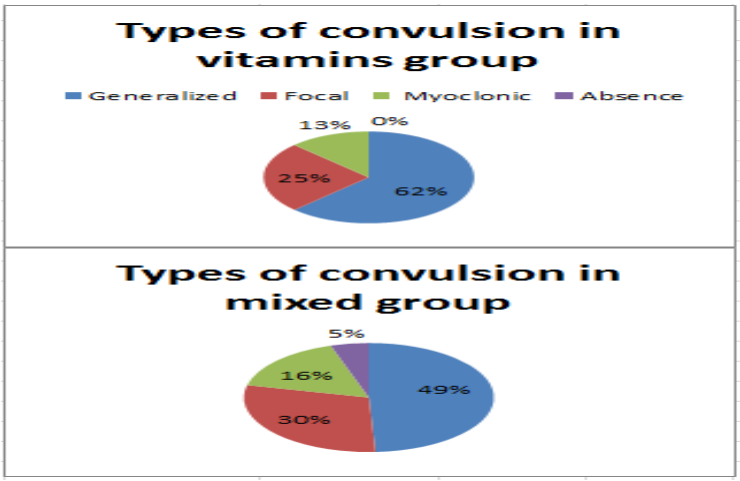

Figure 1: Types of convulsions in the two studied groups

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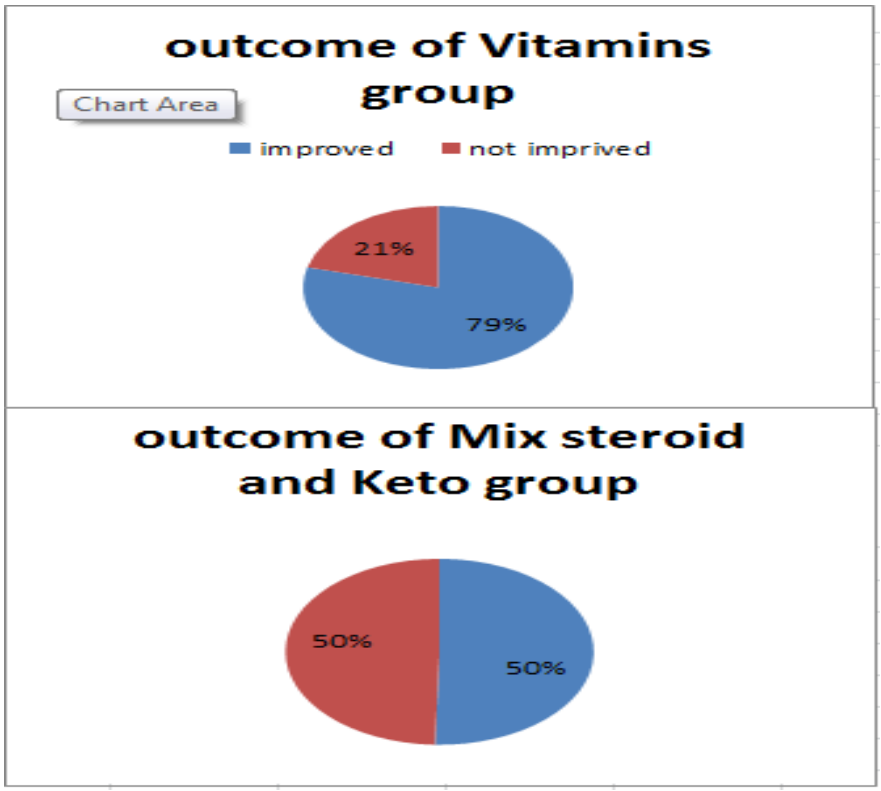

Figure 2: Outcomes in the two studied groups after treatment protocol

Table (1): Comparison of Demographic data between the studied groups

Variable name	Vitamins group	Mix steroid and Keto group	P value
Age (years) at enrollment to study • Mean± SD • Median (range)	 4.69±2.85 4 (1.5 – 12)	 5.77±2.04 5 (2 – 11)	0.083
Age at start treatment (years)	0.5 (2 mon-12)	1 (1 mon-5)	0.093
Duration of use of antiepileptic drugs (years)	2.6 (at birth-9.5)	4.5 (at birth-9)	0.038
Sex • Male • Female	 21 (60.0) 14 (40.0)	 20 (57.1) 15 (42.9)	0.611
Family history of epilepsy • No • Yes	 21 (60.0) 14 (40.0)	 15 (42.9) 20 (57.1)	0.016

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Consanguinity status			0.025
• No	7 (20.0)	13 (37.1)	
• Yes	28 (80.0)	22 (62.9)	

Quantitative data are presented as mean± SD and median (range), qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table (2): Neurological assessment between the studied groups

	Vitamins	Mix steroid and Keto	P value
Developmental problems			0.63
• Normal	25 (71.4)	30 (85.7)	
• Abnormal	10 (28.5)	5 14.3)	
▪ Delay	9 (90)	3 (8.6)	
▪ Regression	1 (10)	2 (5.7)	

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$

Table (3): Results of laboratory data done for the studied participants according to the treatment protocol

Laboratory data	Vitamins	Mix steroid and Keto	P value
Glucose			0.190
• Mean± SD	76.83± 12.68	85.14±17.44	
• Median (range)	80 (40-98)	80 (60-140)	
Ammonia			0.235
• Mean± SD	62.46±10.36	68.57±15.25	
• Median (range)	60 (45-60)	70 (40-100)	
Lactate			0.343
• Mean± SD	13.49±4.85	12.83±4.32	
• Median (range)	12 (6-30)	12 (7-30)	
RFT			0.65
• Normal	29 (82.9)	30 (85.7)	
• Raised	6 (17.1)	5 (14.2)	
ABG			0.71
• Normal	32 (91.4)	33 (94.2)	
• Acidosis	3 (8.5)	2 (5.7)	
Lipogram			0.07

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• Normal	31	(88.6)	33	(94.2)	
• Increased	4	(11.4)	2	(5.7)	
Metabolic					--------
• Normal	31	(88.6)	31	(88.6)	
• FA oxidation defect	2	(5.7)	2	(5.7)	
• Organic acidemia	2	(5.7)	2	(5.7)	

LFT: liver function tests; RFT: renal function tests; FA: Fatty acid. Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table (4): comparison of radiological findings between the studied groups

Imaging	Vitamins Group		Mix steroid and Keto Group		P value
CT brain					
Normal	25	(54.28)	31	(88.5)	
Abnormal finding	10	(11.4)	4	(11.4)	0.26
• Atrophy	4	(22.9)	3	(8.6)	
• Dandy walker	2	(5.7)	0	(0.0)	
• Hypoxic ischemic	2	(5.7)	1	(2.9)	
• Encephalomalacia	0	(0.0)	0	(0.0)	
• Tuberous sclerosis	2	(5.7)	0	(0.0)	
• Hydrocephalus	0	(0.0)	0	(0.0)	
• Hemiatrophy	2	(5.7)	0	(0.0)	
MRI brain					0.76
Normal	21	(60.0)	26	(74.2)	
Abnormal finding	14	(40.0)	8	(22.9)	
• Atrophy	2	(5.7)	3	(8.6)	
• Dandy walker	2	(5.7)	0	(0.0)	
• Hypoxic ischemic	2	(5.7)	1	(2.9)	
• Encephalomalacia	0	(0.0)	0	(0.0)	
• Demyelination	1	(2.9)	1	(2.9)	
• Mesial temporal	2	(5.7)	2	(5.7)	

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• Encephalitis	0	(0.0)	0	(0.0)	
• Limbic encephalitis	0	(0.0)	0	(0.0)	
• tuberous sclerosis	2	(5.7)	0	(0)	
• Hydrocephalus	0	(0.0)	0	(0.0)	
• Rasmussen encephalitis	2	(5.7)	0	(0.0)	
• Polymicrogyria	1	(2.9)	0	(0.0)	

Qualitative data are presented as number (percentage). Significance defined by $p < 0.05$.

Table (5): Frequency of convulsions from baseline to after treatment among the studied participants according to the treatment protocol

	Vitamins Group	**Mix steroid and Keto group**	**P value[1]**
Baseline convulsion frequency/day			0.952
• Median	8	7	
Follow up convulsion frequency/day			-------
• Median	7	7	
P value[2]	**0.045**	------	
Percent change	**12.5%**	**0.0%**	0.952

Quantitative data are presented as and median (range), and IQR. Significance defined by $p < 0.05$.

P value[1]: for comparing the two studied groups.

P value[2]: for comparing the same group overtime