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COMPARATIVE STUDY OF EFFICACY OF STANDARD TREATMENT VS STANDARD TREATMENT ALONG WITH KETOGENIC DIET IN PEDIATRIC REFRACTORY STATUS EPILEPTICUS

Dr. Saddam Hussain[*1], Dr. Tipu Sultan[2], Dr. Natasha Ghani[3], Dr. Wahab Qadir[4], Dr. Javeria Raza Alvi[5], Dr. Saira Khan[6]

[*1,4]*Fellow Pediatric Neurology Department, The Children's Hospital, UCHS, Lahore*
[2]*Professor / HOD Pediatric Neurology, The Children's Hospital, UCHS, Lahore*
[3,5]*Assistant Professor Pediatric Neurology, The Children's Hospital, UCHS, Lahore*
[6]*Fellow Pediatric Neurology Department, The Children's Hospital, UCHS, Lahore*

[*1]saddamhussain7813@gmail.com, [2]tipusultanmalik@hotmail.com, [3]dr_natasha05@yahoo.com, [4]doc.taimurahmed@gmail.com, [5]drjaveriarazaalvi@gmail.com, [6]dr.sairakhan87@gmail.com

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Refractory status epilepticus, ketogenic diet, seizure control, pediatric neurology, EEG recovery.

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Corresponding Author: *
Dr. Saddam Hussain

Abstract

Objective: *To compare the efficacy of standard anti-seizure treatment alone versus standard treatment combined with the ketogenic diet in children with RSE.*

Study Place: *This Quasi-experimental study was conducted at the Department of Pediatric Neurology, The Children's Hospital, UCHS, Lahore from 1st December 2024 to 8th June 2025.*

Methodology: *42 children aged 1–18 years with RSE were enrolled. All patients were initially managed with standard anti-seizure therapy. Due to inadequate response, KD was introduced approximately 7 days after the onset of status epilepticus. Patients were then divided into two groups: 21 received standard therapy alone, and 21 received adjunctive KD.*

Results: *In the KD group (n = 21), seizure reduction ≥50% was achieved in 16 patients (76.2%), EEG recovery within 7 days in 15 patients (71.4%), and IV midazolam discontinuation within 2 weeks in 16 patients (76.2%). Ketosis was achieved in 18 patients (85.7%) within approximately 2 days. Adverse effects were reported in 11 patients (52.4%), with only one patient requiring discontinuation of KD.*

Conclusion: *Ketogenic diet is a safe and effective adjunct to standard therapy in pediatric RSE. Early KD initiation significantly improves seizure control, EEG recovery, and facilitates midazolam infusion withdrawal. These findings support its timely use in refractory cases.*

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures. Globally, epilepsy affects about 50 million people. Although adequate epidemiological research is lacking for Pakistan, the prevalence of epilepsy is thought to be 9.99/1000 [1]. The most frequent neurological emergency in children is status epilepticus (SE), which has a variable etiology and is linked to a high rate of morbidity and death, especially in cases of refractory and super-refractory SE [2]. Refractory status epilepticus (RSE) is a condition in which the seizures are not controlled by first- or second-line anti-seizure medications, such as benzodiazepines of patients who initially present with status

epilepticus; between 31% and 43% develop RSE, which necessitates coma induction as a form of treatment [3]. The incidence of SE from a study done in Thailand was estimated as 5.10/100,000 population, with an estimated higher incidence in developing countries [4] while another study carried out in united-states quotes 20/100,000 children per year [5]. Patients with RSE/SRSE are not only at increased risk for mortality, but also for neurological and systemic problems due to the extended length of time spent in the intensive care unit and the use of anesthesia. Hypotension, prolonged respiratory failure, sepsis, pneumonia, urinary tract infections, and extended immobility are among the comorbidities associated with intensive care units [6]. Anticonvulsants, anesthesia (ketamine, propofol), immunotherapy (IVIG, Steroids), ketogenic diet, and epilepsy surgery (deep brain stimulation and vagal nerve stimulation) are among the treatment modalities for refractory status epilepticus. Conventional anti-seizure medications (ASMs) have side effects and are not always effective. Despite the development of novel anti-seizure medications (ASMs), approximately 30% of epileptic patients still have uncontrollable seizures or serious adverse effects [7]. Ketogenic diet is a diet containing high fat, low carbohydrate and low protein diet which is used as a therapy for the treatment of refractory epilepsy [8]. Several local studies have also confirmed its efficacy and tolerability in children with refractory epilepsy, highlighting the importance of compliance for better outcomes [9]. Ketogenic diet helps in the production of ketone bodies and the human body uses ketones as a source of energy rather than carbohydrates. It was first used in 1921 for the treatment of epilepsy. Epileptic encephalopathies (such as Dravet syndrome, Doose syndrome, etc.) and GLUT-1 deficiency should be treated with a ketogenic diet [10,11]. On the other hand, beta oxidation defects, small, medium, or large chain acyl dehydrogenase deficiencies, pyruvate carboxylase, primary or secondary carnitine deficiencies, and porphyria are contraindicated [11,12]. The outcome for the use of ketogenic diet for the treatment of refractory epilepsy is found to be good in both children and adults [13]. The goal of this research is to establish clinical evidence by comparing the effectiveness of ketogenic diet with standard treatment in individuals with refractory status epilepticus. To imply that ketogenic diet can be a good alternative treatment for RSE.

Objective:

To compare the efficacy of standard treatment versus standard treatment along with ketogenic diet for management of pediatric refractory status epilepticus.

Methodology:

This Quasi-experimental study was conducted at the Department of Pediatric Neurology, The Children's Hospital, UCHS, Lahore from 1 December 2024 to 8th June 2025. Data were collected through a non-probability purposeful sampling technique. Sample size was estimated as 41 cases using a 90% confidence interval and 5% margin of error taking the incidence of refractory status epilepticus as 3.9/100,000 population using openepi[2]. We collect the data from 42 patients.

INCLUSION CRITERIA:

1. All children from 1 year to 18 years of age of either gender.
2. Patients with refractory status epilepticus irrespective of their aetiology (known epileptics, new onset febrile/afebrile seizures, epilepsy due to neuro-degeneration, stroke, neuro metabolic cause or cerebral palsy).

EXCLUSION CRITERIA:

1. Non-convulsive status epilepticus.
2. Individuals who suffer from beta oxidation impairments, pyruvate carboxylase deficiency, deficits in small, medium, or large chain 2acyl dehydrogenase, deficiencies in primary or secondary carnitine, and porphyria.

Data collection

Following approval from the hospital's Ethical Review Committee IRB#781/CH-UCHS, informed consent was obtained from the parents

or guardians of all eligible participants. Baseline demographic and clinical data were recorded, including age, gender, seizure type, duration of seizure activity, and etiology. The 42 patients were assigned to two groups using a simple lottery method to ensure an approximately unbiased distribution; however, as the participants were drawn from existing patient populations and complete randomization was not possible, the study is classified as quasi-experimental. Group A received standard medical treatment for RSE in accordance with institutional protocols. Group B received standard treatment along with the ketogenic diet. Patients in Group B underwent a detailed metabolic evaluation to rule out contraindications to the ketogenic diet. A multidisciplinary team consisting of a pediatric neurologist, a dietitian, and a ketogenic diet nurse provided structured counseling to the caregivers regarding dietary preparation, measuring food portions, expected complications, and monitoring of urinary ketones and blood glucose. Prior to initiating the diet, patients underwent a battery of investigations including complete blood count, liver and renal function tests, serum electrolytes, anion gap calculation, urine ketone analysis, fasting lipid profile, abdominal ultrasound, and an electroencephalogram (EEG). Anthropometric parameters such as height, weight, and body mass index (BMI) were used to calculate the caloric and fluid requirements, as well as the ketogenic ratio. The diet was introduced with a 48-hour carbohydrate washout phase, Prior to initiation of the ketogenic diet, a washout period of approximately 2 days was implemented. During this period, patients who were NPO had their intravenous dextrose switched to normal saline. This approach was used to minimize the influence of prior therapies and prepare the patients safely for ketogenic diet initiation, followed by progressive advancement through 2:1, 3:1, and ultimately 4:1 fat-to-carbohydrate/protein ratios at 48-hour intervals depending on the patient's clinical tolerance and achievement of ketosis. Upon successful induction of ketosis, the diet was maintained. The clinical response was evaluated based on key outcome measures, including complete cessation of seizures, at least 50% reduction in seizure frequency, reduction in seizure duration, successful withdrawal of midazolam infusion within two weeks, and improvement in EEG background activity. A follow-up EEG was conducted on the seventh day of the ketogenic diet to document electrophysiological changes.

Data Analysis

All data were entered and analyzed using SPSS version 25. Quantitative variables such as age were described using means and standard deviations, while qualitative variables such as gender, seizure control status, and EEG improvement were expressed as frequencies and percentages. To control for potential confounders, such as age and concurrent anti-seizure medication use, post-stratification analysis was performed. The Chi-square test was applied to assess differences in outcomes between the two treatment groups. A p-value of ≤0.05 was considered statistically significant for all comparisons.

Results

Data were collected from 42 patients. The mean age of participants in the KD group was 4.5 ± 3.9 years, compared to 4.26 ± 4.06 years in the standard treatment group, showing comparable age distribution. Gender distribution was nearly equal in both groups, with a slight male predominance in the standard group (52.4%) and female predominance in the KD group (52.4%). Urban residency was more common in the standard group (71.4%) than in the KD group (47.6%). Both groups were otherwise demographically balanced, minimizing potential confounders.

Table 1: Demographic Characteristics of Both Groups

Variable	KD Group (n = 21)	Standard Group (n = 21)
Age (Mean ± SD)	4.5 ± 3.9 years	4.26 ± 4.06 years
Gender		
– Male	10 (47.6%)	11 (52.4%)
– Female	11 (52.4%)	9 (47.6%)
Residence		
– Urban	10 (47.6%)	15 (71.4%)
– Rural	10 (47.6%)	6 (28.6%)

Following the initiation of the ketogenic diet, 76.2% of patients experienced a ≥50% reduction in seizure frequency, while 71.4% achieved EEG background recovery within 7 days. IV midazolam infusion was successfully discontinued in 76.2% of cases, indicating improved seizure control and stabilization. Additionally, 85.7% of patients achieved ketosis within 2 days, demonstrating prompt metabolic response and adherence to dietary intervention.

Table 2: Clinical Outcomes in KD Group (n = 21)

Outcome	Yes (n)	No (n)
Seizure Reduction ≥50%	16	5
EEG Recovery within 7 Days	15	6
IV midazolam infusion Stopped ≤2 Weeks	16	5
Ketosis Achieved ≤2 Days	18	3

Out of 21 patients, 11 (52.4%) experienced adverse effects related to the ketogenic diet, whereas 10 (47.6%) tolerated it without any complications. The most common issues included vomiting with hypertriglyceridemia (14.3%) and isolated hypertriglyceridemia (14.3%). Liver enzyme elevations were noted in two cases, with one patient continuing KD and one requiring discontinuation due to combined hepatic and gastrointestinal symptoms.

Table 3: KD Side Effects (n = 21)

KD Side Effect	Frequency (n)	Percentage (%)
No Side Effects	10	47.6%
Vomiting + Hypertriglyceridemia	3	14.3%
Hypertriglyceridemia Only	3	14.3%
Liver Marker Elevation (LM)	2	9.5%
LM – KD Continued	1	4.8%
LM + Vomiting – KD Stopped	1	4.8%
Total with Side Effects	**11**	**52.4%**

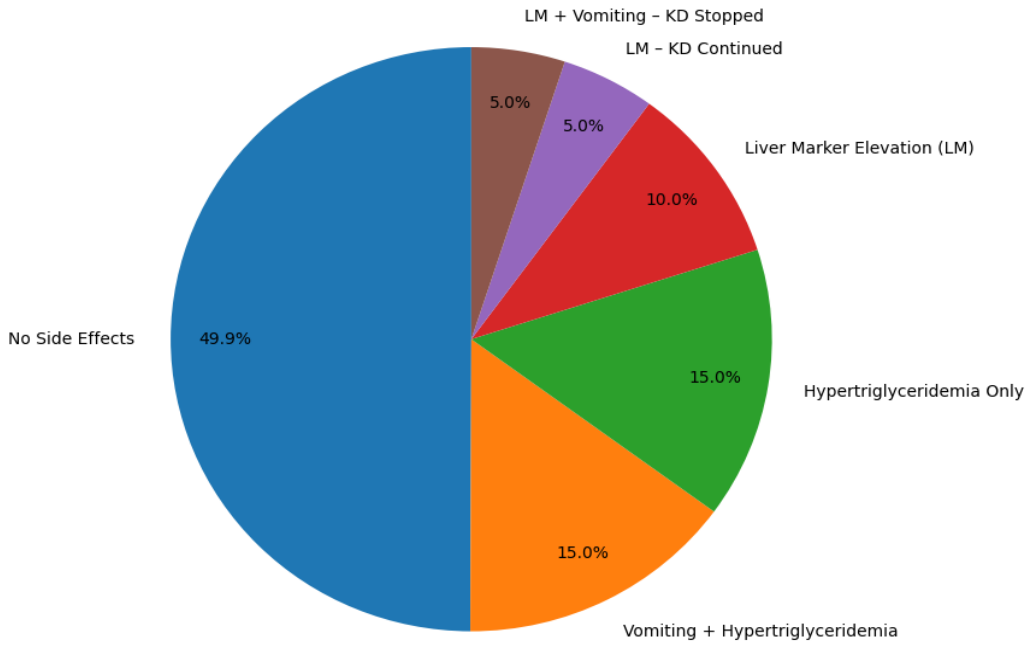


Figure 1: Side effects of KD

Among the 21 patients receiving KD, 16 (76.2%) demonstrated a ≥50% reduction in seizure activity, and 15 (71.4%) showed EEG improvement within 7 days. Conversely, 5 patients (23.8%) had less than 50% seizure reduction, and 6 (28.5%) failed to show EEG normalization.

Table 4: Seizure Control and EEG Recovery in KD Group (n = 21)

Outcome	Frequency (n)	Percentage (%)
Seizure Reduction ≥50%	16	76.20%
EEG Recovery within 7 Days	15	71.4%
Seizure Reduction <50% or No Change	5	23.8%
No EEG Recovery within 7 Days	6	28.5%

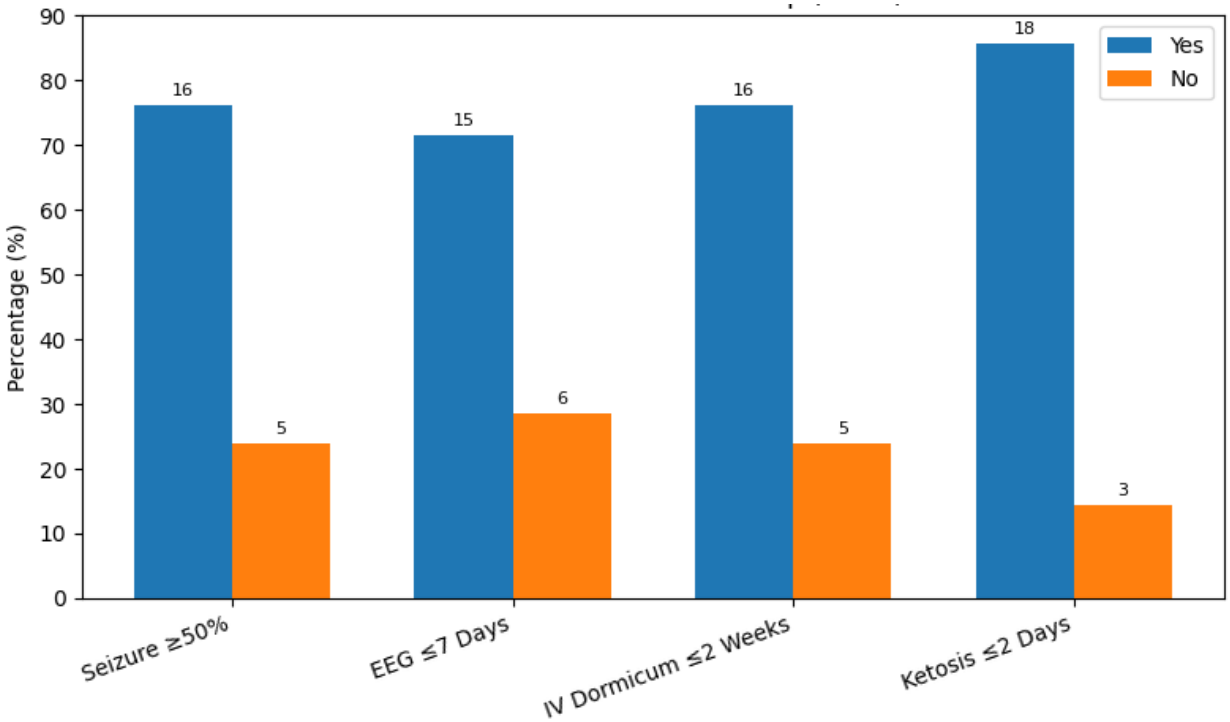


Figure 2: Clinical Outcomes in KD group

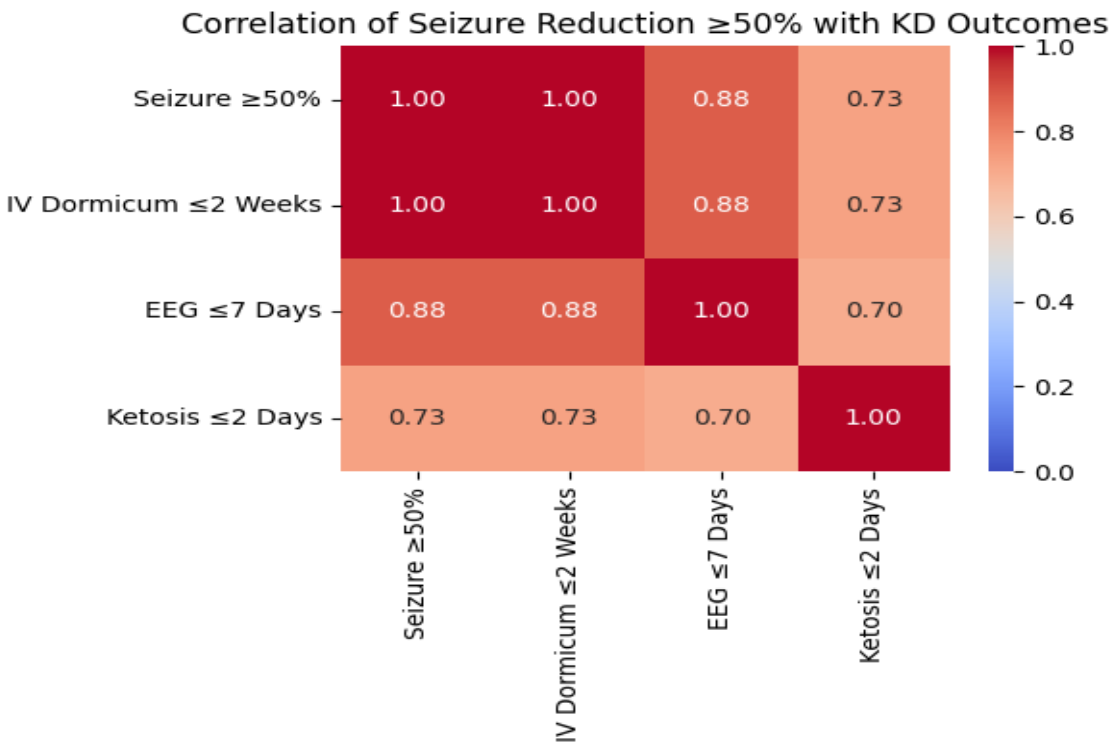


Figure 3: Seizure reduction ≥50% is perfectly correlated with stopping IV Dormicum(midazolam) (r = 1.00) and strongly correlated with EEG recovery ≤7 days (r = 0.88) and ketosis ≤2 days (r = 0.73).

Discussion

In this study, we evaluated the efficacy of the ketogenic diet (KD) as an adjunct to standard anti-seizure therapy in children with refractory status epilepticus (RSE). All patients were initially managed with standard treatment, and due to inadequate seizure control, KD was initiated after an average of 7 days. Following KD initiation, significant clinical improvements were observed, including ≥50% seizure reduction within 7 days in 76.2% of patients, EEG background recovery in 71.4%, and successful discontinuation of intravenous midazolam within two weeks in 76.2% of cases. Ketosis was achieved in nearly all patients (~85%) within 48 hours, reflecting rapid metabolic adaptation and a timely therapeutic response. These findings align with earlier studies that have demonstrated the efficacy of KD in super-refractory and refractory epileptic conditions [14]. Arya et al., (2018) reported comparable seizure control rates and emphasized the role of KD in facilitating anesthetic weaning and improving electrographic parameters. Our results are consistent with these findings, reinforcing KD's role as a metabolic-based intervention capable of modulating neuronal excitability through mechanisms such as enhanced GABAergic activity, ATP-sensitive potassium channel regulation, and anti-inflammatory effects [15].

Our findings indicate that the ketogenic diet is a well-tolerated intervention for pediatric RSE. Although nearly half of our cohort experienced adverse effects most commonly gastrointestinal symptoms and hypertriglyceridemia, these events were largely transient and manageable [16]. The study also highlights that KD can be safely implemented even in complex neurocritical care settings [17,18]. Its ability to produce clinically meaningful seizure reduction within days makes it a viable adjunctive strategy, especially when traditional pharmacologic regimens fail [19].

In refractory epilepsy, therapeutic strategies must balance seizure control with treatment tolerability, as prolonged ASM exposure can be limited by adverse effects and reduced retention [20]. When surgical interventions are not feasible, non-pharmacologic approaches such as vagus nerve stimulation and KD provide alternative treatment pathways [21]. The mechanistic rationale for KD involves ketone-mediated modulation of neuronal excitability, mitochondrial energy metabolism, and anti-inflammatory signaling, which may contribute to neuroprotection [22, 23].

However, a few limitations merit discussion. First, the sample size was relatively small, limiting the generalizability of results. Second, long-term outcomes such as neurodevelopmental status, relapse rates, and cognitive improvement were not assessed. Additionally, while patients were randomized post-standard treatment, the lack of blinding may introduce bias in assessing some clinical outcomes. Despite these limitations, the study offers compelling evidence for the early consideration of KD in pediatric RSE, particularly when seizures remain uncontrolled beyond the initial therapeutic window. Given its metabolic mode of action and relatively safe profile when monitored closely, KD represents a critical tool in the therapeutic armamentarium for neurocritical care units.

Conclusion

It is concluded that the ketogenic diet, when introduced as an adjunct to standard anti-seizure therapy, is an effective intervention for managing pediatric refractory status epilepticus. In this study, KD led to significant seizure reduction (≥50%) in the majority of patients, early EEG recovery, and timely discontinuation of intravenous midazolam infusions. Ketosis was achieved rapidly, within approximately two days of dietary initiation. Although adverse effects were observed in over half of the patients, most were mild and manageable, with only one case requiring discontinuation. These results highlight the clinical utility of KD as a valuable and safe therapeutic option in cases where standard pharmacological treatments are insufficient.

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Conflict of interest: None

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