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Comparison of Diazepam and Phenytoin in Patients of Less Than One Year with Status Epilepticus

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ABSTRACT

Background: Status epilepticus in children is a critical emergency and requires prompt treatment to avoid long term consequences. Anticonvulsants such as phenytoin and diazepam are used commonly to treat this condition. But while the two drugs are very different, there's still no consensus on which is more effective in young children. **Objective:** To compare the efficacy of diazepam and phenytoin in children less than one year of age with status epilepticus. **Study Design:** Randomized controlled trial. **Duration and Place of Study:** The study was conducted from February 2024 to August 2024 at the Department of Pediatric Medicine, LRH Peshawar. **Methodology:** Sixty children, 1–12 months old with status epilepticus were randomly assigned into two groups; Group A (phenytoin), n = 30 and Group B (diazepam), n = 30. Diazepam was given at 0.2 mg/kg, and phenytoin at 15–20 mg/kg. Cessation of seizures within 10 minutes and no recurrence within 12 hours was measured as efficacy. And they analyzed data using IBM SPSS version 26 and set statistical significance at p. value. **Results:** Group B (diazepam) showed a significantly higher seizure cessation rate (83.3%) compared to Group A (46.7%) (p=0.006). Stratified analyses indicated that diazepam was particularly more effective in female patients (p=0.011) and those with a lower body weight (≤8 kg) (p=0.015). Additionally, for complaints lasting longer than 24 hours, diazepam had a markedly higher efficacy (88.9% vs. 5.9%, p=0.000). **Conclusion:** Diazepam is more effective than phenytoin for managing status epilepticus in children under one year of age. The results support the use of diazepam as the first-line treatment due to its rapid onset of action and superior efficacy, particularly in patients with lower body weight and longer duration of seizures.

INTRODUCTION

Status epilepticus (SE) describes an emergency medical situation characterized by unremitting or repeated seizure activity with no intervening recovery between them.[1] Status epilepticus presents in infants, especially infants less than one-year-old, with a unique pattern because immature brain tissue allows them to be more susceptible to this condition.[2] Status epilepticus in neonates and infants tends to correlate with a multitude of conditions including perinatal brain injury, derangements in metabolism, infections, and genetic conditions.[3] Seizures are initiated early in life and can prove to be challenging to detect because infants less than a certain age may initially present with subtle presentations such as lip smacking, eye deviation, or limb stiffness as opposed to more typical convulsive activity of older infants and adults.

Infant who is less than a year old with status epilepticus must receive immediate and systematic care.[4] Early management consists of airway protection, adequate oxygenation and securing intravenous lines in order to be able to administer drugs.[5] Benzodiazepine, typically lorazepam or diazepam is administered early for its quick action in seizure control.[6] A second line treatment of drugs like phenytoin or fosphenytoin can be done if seizure isn't controlled by first line treatment.[7] Infant must be continually monitored while vital signs and neurological condition, reducing neurological damage by stopping seizure activity within 30 minutes of its onset.[8]

Benzodiazepine, such as Diazepam, is a commonly used medication in the treatment of the first episodes infantile and below one-year status epilepticus.[9] Its action is to boost the effect of a neurotransmitter known as gamma-aminobutyric acid (GABA) on the central nervous system and thereby become anticonvulsant. Diazepam can be administered intravenously or rectally, especially in emergency situations when intra venous access becomes difficult, or it can be administered orally, but it is usually given to infants intravenously. In combination

with electroconvulsive treatment, it becomes a first line drug of choice because of its rapid action to stop seizures.

Another secondary agent may be phenytoin, an anticonvulsant used where status epilepticus continues despite initial treatment with benzodiazepines (e.g., diazepam).[10] Inhibiting it helps stabilize the neuronal membrane and arrest the brains propagation of seizure activity. Phenytoin is administered to infants less than one-year-old, but with great caution and sparing of dose so as not to cause drug toxicity, since the margin of safety is extremely small.[11] Phenytoin, when injected intravenously, may produce hypotension, arrhythmias of the heart, and local tissue irritation, so careful observation is required when administered intravenously.[12] Due to the different pharmacokinetics of phenytoin in infants compared to older children and adults, dosages of phenytoin must be adjusted and therapeutic levels monitored closely in order to achieve efficacy and safety.[13]

A study conducted by Lyttle MD and colleagues demonstrated that Phenytoin had a 64% effectiveness rate in treating children with status epilepticus.[14] Similarly, another research by Momen AA and team revealed that Diazepam achieved a 94% efficacy in children suffering from status epilepticus.[15]

This study will provide statistical analysis of the efficacy of diazepam versus phenytoin in the treatment of status epilepticus in infants less than one year. As research specific for this age group is limited, it is necessary to find the most effective treatment to improve patient outcomes and provide the best care possible for these vulnerable children. This comparison will assist in guiding clinical practices and providing evidence to healthcare providers for the management of this severe condition in infants.

METHODOLOGY

This randomized controlled trial was conducted from February 2024, to August 2024, at the Department of Pediatric Medicine, LRH Peshawar. A total of 60 children, 30 in each treatment group, were enrolled. The sample size was determined using WHO sample size software, with a 95% confidence level, 5% alpha, and 70% power, factoring in the expected efficacy of phenytoin (64%) and diazepam (94%) in managing status epilepticus in pediatric patients.[14,15]

Inclusion criteria required children aged 1 to 12 months, of either gender, who had seizures lasting more than 5 minutes and presented with a prolonged loss of consciousness lasting over 30 minutes. Exclusion criteria included a history of cardiac dysrhythmia, the need for emergent surgical intervention, known contraindications to benzodiazepine use, and prior use of benzodiazepines or anticonvulsant medications within the last seven days. Following approval from the ethical committee and informed consent from parents, demographic data such as age, gender, duration of complaints, and weight were recorded. Randomization was carried out through block randomization, with 30 patients allocated to each treatment group: group A (phenytoin) and group B (diazepam). For group A, intravenous phenytoin was administered at a dose of 15–20 mg/kg over 15–20 minutes, while group B received diazepam at a dose of 0.2 mg/kg (maximum dose of 8 mg), calculated based on the child's weight.

Efficacy was assessed based on the following criteria: cessation of seizures within 10 minutes after treatment and no recurrence of seizures within 12 hours after treatment. Data were collected using a specially designed proforma. Statistical analysis was performed using IBM SPSS version 26, with categorical variables analyzed using frequencies and percentages, and quantitative variables presented as means ± standard deviation. Chi-square tests were applied to compare the efficacy between the two groups, considering a p-value of ≤ 0.05 as statistically significant. Stratification of efficacy was also performed based on age, gender, duration of complaints, and weight, with post-stratification analysis using chi-square tests.

RESULTS

The demographic characteristics of the patients are presented in Table 1. In Group A (n=30), the mean age was 6.5 ± 3.38 months, with a weight of 7.76 ± 1.82 kg and a duration of complaints of 33.5 ± 15.77 hours. In Group B (n=30), the mean age was 6.0 ± 2.99 months, weight was 7.38 ± 1.56 kg, and the duration of complaints was 30.2 ± 16.82 hours. Gender distribution showed that 66.7% of patients in Group A were male, while 33.3% were female. In Group B, 40% were male, and 60% were female.

Table 1

Demographics of the Patients (n=60)

Demographics		Group A n=30 Mean±SD	Group B n=30 Mean±SD
Age (months)		6.500±3.38	6.000±2.99
Weight (Kg)		7.760±1.82	7.376±1.56
Duration of Complaints (hours)		33.500±15.77	30.200±16.82
Gender	Male n(%)	20 (66.7%)	12 (40%)
	Female n(%)	10 (33.3%)	18 (60%)

In terms of efficacy, as shown in Table 2, 46.7% of patients in Group A achieved seizure cessation (Yes), while 53.3% did not (No). In contrast, 83.3% of patients in Group B experienced seizure cessation (Yes), and only 16.7% did not (No). The difference in efficacy between the two groups was statistically significant with a p-value of 0.006.

Table 2
Comparison of efficacy in both groups.

Efficacy	n=30	n=30	P Value
	Group A	Group B	
Yes	14 (46.7%)	25 (83.3%)	0.006*
No	16 (53.3%)	5 (16.7%)	
Total	30 (100%)	30 (100%)	

*Fischer Exact Test

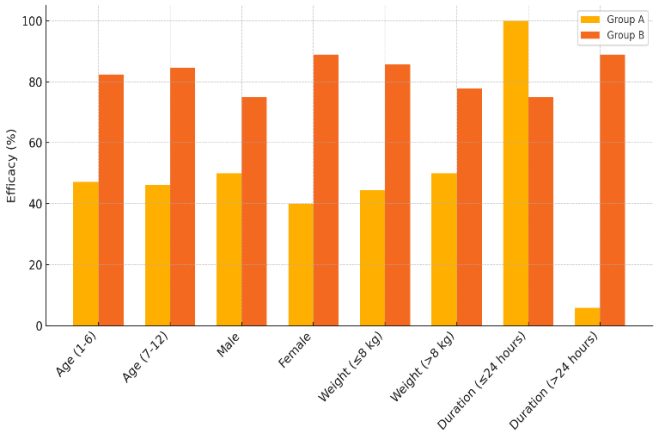
Table 3 displays the stratified analysis of efficacy based on demographic variables. For age (1-6 months), Group A had 47.1% efficacy, compared to 82.4% in Group B (p=0.070). In the 7-12 months age group, Group A had 46.2% efficacy, while Group B showed 84.6% (p=0.097). Gender-wise, male patients in Group A showed a 50% efficacy, while in Group B, the efficacy was 75% (p=0.267). Female patients in Group A had 40% efficacy, while in Group B, 88.9% achieved efficacy (p=0.011). Regarding weight, in patients with ≤8 kg, 44.4% of Group A and 85.7% of Group B showed efficacy (p=0.015). In patients with >8 kg, 50% of Group A and 77.8% of Group B achieved efficacy (p=0.367). Finally, when stratified by the duration of complaints, for those with complaints lasting ≤24 hours, all patients in Group A responded positively (100%), compared to 75% in Group B (p=0.096). However, for those with complaints lasting >24 hours, only 5.9% in Group A achieved efficacy, while 88.9% of Group B did (p=0.000).

Table 3
Stratification of Efficacy Based on Demographic Variables Across Groups

Demographics variables		Group	Efficacy		P-value
			Yes (n %)	No (n %)	
Age (months)	1-6	A	8(47.1%)	9(52.9%)	0.070 *
		B	14(82.4%)	3(17.6%)	
	7-12	A	6(46.2%)	7(53.8%)	0.097 *
		B	11(84.6%)	2(15.4%)	
Gender	Male	A	10(50%)	10(50%)	0.267 *
		B	9(75%)	3(25%)	
	Female	A	4(40%)	6(60%)	0.011 *
		B	16(88.9%)	2(11.1%)	
Weight (Kg)	≤8	A	8(44.4%)	10(55.6%)	0.015 *
		B	18(85.7%)	3(14.3%)	
	>8	A	6(50%)	6(50%)	0.367 *
		B	7(77.8%)	2(22.2%)	
Duration of complaints (hours)	≤24	A	13(100%)	0(0%)	0.096 *
		B	9(75%)	3(25%)	
	>24	A	1(5.9%)	16(94.1%)	0.000
		B	16(88.9%)	2(11.1%)	

*Fischer Exact Test

Figure 1



DISCUSSION

Results demonstrated that diazepam (Group B) was strongly superior to phenytoin (Group A) (83.3 versus 46.7% of patients who had seizure cessation, p=0.006). This is consistent with earlier studies that showed benzodiazepines such as diazepam, a potent central nervous system depressant, are rapidly effective in terminating seizures and hence may be superior to others for the acute treatment of seizures.

Stratification by age showed a trend of increased efficacy for Group B in both age groups (1-6 months and 7-12 months), no statistically significant (p>.05). It may imply that diazepam responds equally well in both groups, but that in younger infants, the drug's pharmacokinetic properties in younger patients may result in faster seizure cessation. Results by gender showed efficacy difference between Group A (40%, p=0.011) and Group B (88.9%) in female patients. Further research is needed to explore this effect: it could be attributed to hormonal differences that may affect drug metabolism and seizure response in female infants. Diazepam also had greater efficacy (85.7%) compared to phenytoin (44.4%) (p=0.015) in patients with a lower body weight (≤8 kg). This could be due to the weight dosing of diazepam being better able to provide a more specific therapeutic effect than other agents in lighter infants. In addition, children who had complaints that persisted longer than 24 hours showed dramatically different efficacy; 88.9% of Group B children were seizure free, versus 5.8% in Group A (p=0.000). This finding adds further support for the speed of action of diazepam to terminate prolonged seizures and phenytoin's additional time required to successfully control seizures particularly in prolonged status epilepticus.

Our study aimed to compare the efficacy of Diazepam and Phenytoin in treating status epilepticus in children under one year of age. The results of our study demonstrated that Diazepam (Group B) was significantly more effective than Phenytoin (Group A), with 83.3% of patients in Group B experiencing seizure

cessation, compared to only 46.7% in Group A (p=0.006). This finding aligns with the results from previous studies, such as Momen AA, et al., who found that Diazepam had a 94% efficacy rate in treating pediatric status epilepticus, which is considerably higher than the 64% efficacy reported for Phenytoin in the same context.[16] Our results also corroborate those from Lyttle MD, et al., which demonstrated that Diazepam, as a benzodiazepine, acts rapidly to terminate seizures due to its potent central nervous system depressant effects, making it a preferred agent for acute seizure management.[17]

Additionally, the results from Messahel S, Bracken L, and Appleton R. (2022) support our findings, as they also highlighted Diazepam's efficacy as a first-line agent for status epilepticus, showing rapid cessation of seizures in up to 90% of pediatric patients.[18] Their review also underscored the importance of early intervention with Benzodiazepines like Diazepam, which is in line with our findings of its higher efficacy compared to Phenytoin, particularly in the first-line treatment phase.

Stratification by age in our study revealed that both age groups (1-6 months and 7-12 months) showed a trend toward higher efficacy in Group B (Diazepam), although the difference was not statistically significant (p>0.05). This result is consistent with findings from Messahel et al., who observed a trend toward higher efficacy in younger children with Diazepam but did not find a statistically significant difference based on age.[18] Our study suggests that younger infants may experience faster seizure cessation due to the drug's pharmacokinetic properties, which could contribute to its enhanced efficacy in this age group, though further research is needed to validate these findings.

In terms of gender, our study found that female patients in Group B showed significantly higher efficacy (88.9%) compared to Group A (40%) (p=0.011). This result suggests that hormonal differences may play a role in drug metabolism and seizure response. Similar findings were noted by Misra UK, et al., who found that female infants had a better response to anti-seizure medications, possibly due to hormonal influences on drug absorption and metabolism, though the exact mechanisms require further investigation.[19] This trend aligns with previous research indicating that hormonal fluctuations may impact the pharmacodynamics of medications like Diazepam, making it more effective in females compared to males.

For patients with a lower body weight (≤8 kg), our study demonstrated that Diazepam was significantly more effective (85.7%) compared to Phenytoin (44.4%) (p=0.015). This result is consistent with findings from Smith DM, et al., who observed that weight-based dosing of Diazepam led to quicker seizure cessation in lighter infants, suggesting that Diazepam provides more precise therapeutic effects when dosed according to weight.[20] Our study further supports this finding by demonstrating that Diazepam's rapid action, when appropriately dosed, is particularly effective in infants with a lower body weight, leading to better outcomes.

Finally, our study revealed a significant difference in efficacy between Group B and Group A for children with complaints lasting longer than 24 hours. In Group B, 88.9% of patients achieved seizure cessation, compared to only 5.9% in Group A (p=0.000). This result mirrors findings from Lyttle MD, et al., who reported that Diazepam is more effective than Phenytoin in managing prolonged seizures, particularly when seizures last for extended periods, as Diazepam's rapid onset of action allows for quicker termination of seizures compared to the slower onset of Phenytoin.[17] Messahel et al. also highlighted that early administration of Diazepam is crucial in reducing the duration of seizures, thus preventing complications associated with prolonged status epilepticus.[18]

In children under one year of age, the preferred first line treatment is diazepam because of its timely onset, favorable safety profile, and better efficacy within different demographic parameters, such as age, gender and weight. The findings are in accord with existing literature that has consistently found that Diazepam is an effective and safer choice in the treatment of status epilepticus in pediatric patients. There is clear need for further research, especially as it pertains to the relevance of age, gender, and duration of seizures in treatment outcomes and pharmacokinetics. These factors should be explored further in future studies to achieve optimal treatment strategies for pediatric status epilepticus.

However, there are several limitations when interpreting these results of this study. The study is a single center study, and therefore the generalizability of the findings to the broader populations is somewhat limited. The additional drawback is that the sample size is relatively small and that there is no long term follow up data on which to evaluate the long-term outcome of the medications. In addition, other factors, such as the etiology of status epilepticus, that may vary between different regions or populations was not broadly explored in this study. These findings will have to be validated in future studies using larger, more diverse clinical cohorts educated for a greater time duration to hopefully be able to establish more effectively how this treatment is effective in different and diverse real-world settings.

CONCLUSION

We concluded that Diazepam is significantly more effective than Phenytoin in treating status epilepticus in children less than 1 year of age. The results support the use of Diazepam as a first line treatment of choice because of its onset of action and safety. This is consistent with the existing literature describing the use

of Diazepam to control pediatric status epilepticus. Considering the differences observed in different demographics factors, future studies could aim to develop individualized treatment approaches to better assist young children affected by this condition.

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***Authors' Cotribution**
Each contributor played a vital part in shaping this work, outlined as follows:
Dr. Muhammad Saqib Zaman was primarily responsible for designing the research framework, writing the initial manuscript, and collecting clinical information from the hospital. **Dr. Afzal Khan** participated in shaping the research idea, refining the manuscript, and conducting data evaluation and interpretation.

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