

Efficacy of Acetazolamide in Refractory Epilepsy Management: A Quasi-Experimental Study

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ABSTRACT

Objective: To assess the efficacy of Acetazolamide in refractory epilepsy management.

Study Design: Quasi-experimental study.

Place and Duration of Study: Outpatient Neurology Department, Allied Hospital, Faisalabad Pakistan, from Sep 2020 to Feb 2021.

Methodology: Using a non-probability consecutive sampling technique, 260 patients of either gender aged 18 to 60 years who met the criteria of refractory epilepsy were included in the study. Group-A (n=130) received oral Acetazolamide (250 mg twice a day) plus standard antiepileptic drugs, and Group-B (n=130) received a placebo plus standard antiepileptic drugs. Patients were assessed every four weeks for a six-month response to treatment. The outcome was assessed in terms of control of refractory epilepsy.

Results: Acetazolamide was effective in 88(68.2%) patients compared to Placebo Group, which showed efficacy in 41(31.8%) patients (p -value was <0.001). In addition, the mean change in the number of attacks after treatment was significantly different between Group-A (2.9 ± 1.5) versus Group-B (1.6 ± 1.6) (p -value <0.001).

Conclusion: Acetazolamide is effective in treating refractory epilepsy.

Keywords: Acetazolamide, Efficacy, Refractory epilepsy.

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INTRODUCTION

Epilepsy is one of the most common neurological diseases with high prevalence. Worldwide about 50 million people are affected by epilepsy, of which 80% live in low and middle-income countries.¹ Available data in Pakistan showed that epilepsy is 9.99/1000 population.² Refractory epilepsy is described as uncontrolled seizures regardless of the two tolerated and properly selected antiepileptic drugs (AEDs) applied in combination or as monotherapies.^{3,4} Uncontrolled seizures increase morbidity and mortality risk, such as psychiatric comorbidities like depression, physical trauma due to falls and injuries resulting from seizures, and increased general mortality due to sudden death in epilepsy (SUDEP) and accidents.^{5,6}

The AED should be used for a considerable period, appropriately chosen for the patient's seizure type, and be prescribed at an adequate dose. There is no standardized time duration for a drug to be used before considering it ineffective, but a minimum of 6 months is believed to be necessary.⁷ Predictors of refractory epilepsy are high seizure frequency at onset, focal EEG slowing, history of status epilepticus, structural brain lesions, mental retardation and increased attempts of failed drug therapies etc.⁸

It is commonly used in altitude illness, raised intraocular pressure, familial periodic paralysis, and hydrocephalus.⁹ It has been used for epilepsy since 1953, mainly in combination therapy with other antiepileptic drugs in children and adults.¹⁰ However, refractory epilepsy always remains a key challenge for neurologists. With the advent of new antiepileptic drugs, older drugs like Acetazolamide are rarely used nowadays; however, in refractory cases, the trial of such drugs can be used to control seizures, as studies showed it is effective in both focal and generalized seizures. Therefore, we conducted this study to look for the efficacy of this forgotten but easily available drug in refractory cases because alternative treatments are impenetrable for most patients.

METHODOLOGY

The quasi-experimental study was conducted at the Outpatient Department of Neurology, Allied Hospital, Faisalabad Pakistan, from September 2020 to February 2021. The study was approved by the Institutional Ethical Review Committee (Reg. No.1049, Dated 22/08/2020). With a prevalence of 21.5%,¹¹ the sample size was calculated.

Inclusion Criteria: Patients of either gender aged 18 to 60 years who met the criteria of refractory epilepsy were included in the study by using a nonprobability consecutive sampling technique.

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Exclusion Criteria: Patients with decompensated liver disease, end-stage renal disease, on Aspirin, Topiramate, Sulfonamides, Loop and Thiazide Diuretics, pregnant, lactating mothers, and known hypersensitivity to Acetazolamide were excluded from the study.

Patients were divided into two groups. Group- A was given Acetazolamide (250 mg/PO/BD) plus other antiepileptic drugs, and Group- B received a placebo plus other antiepileptic drugs. The antiepileptic drugs (patients already using) were added according to standard guidelines of refractory epilepsy management. Patients were assessed every four weeks for six months by treating physicians. Drug compliance was assessed by reviewing patients' or their caregivers' monthly drug compliance charts. Efficacy was defined as a decrease in seizure frequency by 50% or more from baseline.

Statistical Package for Social Sciences (SPSS) version 26 was used for data analysis. Qualitative data were presented as frequencies and percentages. Quantitative data were presented as means and standard deviations. Chi-Square and Mann-Whitney U tests were applied. The *p* value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 260 patients were included in this study. The mean age of the patients was 31.87 ± 11.75 . Numbers of monthly seizure attacks at baseline and at the end of the study were 6.3 ± 1.6 vs. 4 ± 1.82 , respectively. Overall primary generalized tonic-clonic seizures were the most common $n=81(31.2\%)$, followed by Secondary generalized tonic-clonic seizures $n=67(25.8\%)$ and others (Table-I).

Table-I: Characteristics of Study Population (n=260)

Study Parameters	n(%)
Age	31.87 ± 11.75
Gender	
Male	145(55.8%)
Female	115(44.2%)
Type of seizures	
Primary generalized tonic clonic seizures	81(31.2%)
Secondary generalized tonic clonic seizures	67(25.8%)
Focal onset impaired awareness	53(20.4%)
Focal onset intact awareness	33(12.7%)
Myoclonus	16(6.2%)
absent seizures	10(3.8%)
Number of attacks of seizures before starting new treatment/ month	6.3 ± 1.6
Number of attacks of seizures 24 weeks after new treatment	4 ± 1.82
Change in number of attacks	2.3 ± 1.71

The efficacy of Acetazolamide and placebo was compared using the chi-square test. The Treatment Group showed drug efficacy in 88(62.8%) patients versus drug efficacy among 41(31.8%) patients in the Placebo Group, ($p < 0.001$). There was a significant difference in the mean change in the frequency of attacks between the two groups ($p < 0.001$) (Table-II).

Table-II: Comparison of Efficacy of Acetazolamide & Placebo in Refractory Epilepsy (n=260)

	Group-A (n=130)	Group-B (n=130)	p-value
Efficacy	88/130(68.2%)*	41/130 (31.8%)*	
Types of Epilepsy	Primary Generalized Tonic Clonic Seizures: 35 (26.9%)	Primary Generalized Tonic Clonic Seizures: 46 (35.3%)	0.000*
	Secondary Generalized Tonic Clonic Seizures: 34 (26.1%)	Secondary Generalized Tonic Clonic Seizures: 33 (25.3%)	
	Focal onset impaired awareness: 30(23%)	Focal onset impaired awareness: 23 (17.6%)	
	Focal onset intact awareness: 15 (11.5%)	Focal onset intact awareness: 18(13.8%)	
	Myoclonus: 12(9.2%)	Myoclonus: 4(3.0%)	
	Absence Seizure: 4(3.0%)	Absence Seizure: 6(4.6%)	0.215
Change in Frequency of Attacks	Mean: 2.97 ± 1.50	Mean: 1.6 ± 1.63	0.000E

change in frequency of attacks was defined as a change in seizure frequency per month from baseline with treatment for each case

Side effect Profile of Acetazolamide during the study showed headache in 10(8%), diarrhoea in 7(5%), malaise and dizziness in 3(2%), and blurring of vision in 2(1%) patients. Different types of seizures in resistant epilepsy are shown in the Figure.

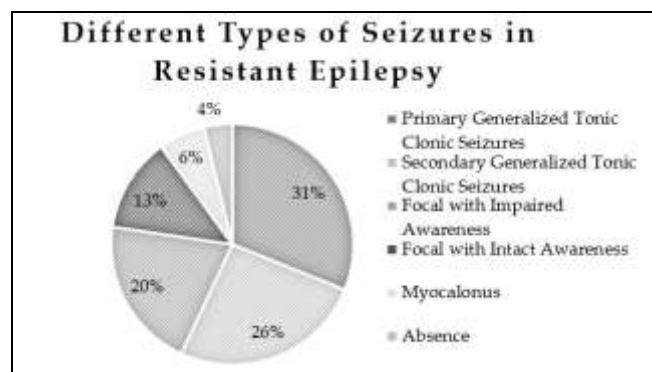


Figure: Different Types of Seizures in Resistant Epilepsy (n=260)

DISCUSSION

Epilepsy is a global disease with an unequal distribution, and about 80% of the affected individuals reside in low and middle-income countries.¹² Epilepsy is a treatable condition with a good therapeutic response. About 70% of patients with epilepsy are controlled with antiepileptic drugs (AED).^{13,14}

In a study on nontraditional drugs in epilepsy by Turner *et al.* there was $\geq 50\%$ seizure reduction in 40–80% of subjects having focal or generalized seizures with uncontrolled Acetazolamide with traditional antiepileptic drugs. It is worth considering medication when traditional drugs fail to control seizures.¹⁵ Resor *et al.* (1990) demonstrated that Acetazolamide was effective in juvenile myoclonic epilepsy patients who also had generalized tonic-clonic seizures. Out of 34 patients, seizures were controlled in¹⁵ patients.¹⁶ The results of our study are also similar in this context, as our study had cases of both generalized and myoclonic epilepsies, and almost two-thirds of our patients had seizure reduction with Acetazolamide.

Evidence in favour of Acetazolamide from studies done on epilepsy in specific population subsets is also abundant in the literature.¹⁷ Acetazolamide was used as adjuvant therapy on 48 patients with childhood absence epilepsy by Hitris *et al.* (2005), 35% participants showed 99% reduction in seizures and 48% showed 90% reduction over one year on Acetazolamide.¹⁸ In their study on 20 female patients with catamenial epilepsy, Verrotti *et al.* (2012) showed a 30%–40% improvement in the frequency and severity of seizures with Acetazolamide.¹⁹ These studies highlight Acetazolamide's overall role in diverse patient populations with different seizure types.²⁰ Our study also had a wide range of age groups and seizure types. The response rate in our study (68.2%) is also comparable with the abovementioned studies.

In our study, 88(68.2%) patients in Group-A experienced a 50% or more reduction in seizure frequency from baseline compared to 41(31.8%) patients in Group- B with few side effects. Compared to the abovementioned studies, the drug was used in a larger group of patients with different seizure types. The *p*-value calculated was significant ($p < 0.001$). Older antiepileptic drugs continue to play a major role in treating epilepsy. Acetazolamide has not been widely used in refractory epilepsy. In light of our findings, we, therefore, suggest the use of Acetazolamide for refractory cases of epilepsy where appropriate.

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CONCLUSION

This study showed that Acetazolamide is beneficial in reducing the frequency of seizures in patients with drug-resistant epilepsy in the local population. Therefore, it is reasonable to use this drug before going for other costly and invasive therapies where appropriate. However, further research is needed for its benefit in a larger population.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MAZ & NA: Critical review, drafting the manuscript, interpretation of data, approval of the final version to be published.

JI & MA: Conception, study design, drafting the manuscript, approval of the final version to be published.

BR: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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