JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/13909

Comparative effectiveness-safety of conventional versus newer antiepileptics in epileptic patients in a tertiary care hospital, India

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Received: 2023-08-29.
Accepted: 2023-10-27

J Clin Med Kaz 2023; 20(6):50-54

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Abstract

Background: As initial monotherapy, individuals with epilepsy are treated with both conventional and newer antiepileptic drugs (AEDs). The differences in their relative effectiveness and safety as a group, however, have not been thoroughly studied.

Objective: To evaluate and compare the effectiveness and safety of conventional and newer anti-epileptic drugs in epileptic patients.

Material and methods: A prospective comparative study was done in 126 epileptic patients. Patients divided into two groups Group A and B of 63 each received conventional and newer antiepileptic drugs respectively. Patients were allocated the AED based on type of epilepsy, patient characteristics and drug characteristics by the treating physician. Patients maintained a seizure diary which they filled weekly and this seizure diary was evaluated at 6 weeks and 12 weeks of follow up. Patients were assessed for adverse drug reactions (ADRs) at 0, 6 and 12 weeks of follow up and also for spontaneous reported ADRs at any time during the study.

Results: In both group A and group B, our study demonstrated that seizure freedom, seizure severity, and time before first seizure did not differ significantly ($p>0.5$). Except for cognitive dysfunction, impaired memory, and swollen gums, which were more frequent in the conventional anti-epileptics group, the ADR profiles of both group of medications were similar. Phenytoin was found to cause gum swelling and cognitive impairment. No subject experienced a serious adverse event.

Conclusion: Newer Antiepileptics as monotherapy are equally efficacious as conventional antiepileptics but may offer a better safety profile to epileptic patients.

Keywords: newer, conventional, antiepileptic drugs, effectiveness, safety

Introduction

A brain function disease known as epilepsy is characterised by the unpredictable and recurrent occurrence of seizures [1]. A comprehensive review and meta-analysis of incidence data revealed that epilepsy has a pooled incidence rate of 61.4 per 100,000 person-years [2]. People of all ages, genders, races, social backgrounds, and geographic areas can develop epilepsy. In India, there are reportedly around 10 million PWE (persons with epilepsy). In our demographic, it affects roughly 1% of people [3].

The widespread familiarity, established effectiveness, typically inexpensive cost, and well-documented ADRs of conventional AEDs have led to their widespread use. However, the 20–25% of patients who experience treatment failure have sparked intense research to create new AEDs [4]. In the treatment of epilepsy, monotherapy is preferred over polytherapy since it is equally or more effective, cost-efficient, and has fewer ADRs [5]. In addition to seizure freedom and control, the safety profile of the medications used for therapy is crucial when it comes to epilepsy [6]. To

prevent seizure recurrence, the AEDs are frequently given orally over a lengthy period of time. To treat their crippling illness and improve their quality of life, epileptic patients will receive the best care possible if their safety profiles are better understood [7].

The AEDs have been divided as per the year of market introduction before or after 1990 into newer and conventional [8]. Numerous studies on the effectiveness of conventional and newer AEDs have failed to show a significant difference. The assertion of an improved safety profile is largely to blame for the current trend of preferring newer AEDs [9]. Before the study's foundation was laid, there were relatively few research evaluating the effectiveness and safety of older and newer AEDs both internationally and among Indian populations. Therefore, the goal of the current study was to examine the safety and effectiveness profiles of conventional and newer AEDs in individuals with epilepsy.

Material and methods

Patients who visited the Neurology Outpatient Department were the subjects of this study. In this prospective, open-label study, 120 individuals were enrolled who were classified as having epilepsy by the International League Against Epilepsy (ILAE) [10] The institutional ethics committee gave its approval to the project.

Inclusion criteria

People of either gender aged 18 to 75 years, classified as epileptics as per the ILAE [10]. Patients who were ready to provide written, fully informed consent.

Exclusion criteria

Patients with progressive or uncontrolled diseases involving central nervous system, heart like progressive encephalopathy, cardiac dysrhythmia, recent myocardial infarction (MI), or congestive heart failure (CHF) or mental illness [11]. Also, people with known hypersensitivity to any study medication or those participating in another study within 8 weeks of study's start date or at any point in the study were excluded. People with known abnormal liver or kidney function (AST (Aspartate transaminase) and ALT (Alanine transaminase) levels above 2 times the upper normal limit) or known abnormal renal function (serum creatinine > 1.5 mg/dL). Pregnant and lactating mothers or people with drug or substance of abuse induced seizures.

According to the ILAE classification, patients with epilepsy (both new and old) were enrolled and split into two groups. Each group had 63 patients in it. It is recommended to discontinue the medication, post two years of seizure freedom [12]. Keeping this in mind, our study, did not have a washout period as we considered it unethical. Moreover, this research was a baseline study and a larger scale research is to be planned with a possible consideration of washout period keeping in mind the frequency of seizures. Each patient got a thorough physical examination and laboratory evaluation. We assessed the heart rate and blood pressure while sitting. Patients in group A were given the conventional AEDs (sodium valproate, carbamazepine, and phenytoin) as monotherapy, whereas those in group B were given the newer AEDs (levetiracetam, oxcarbazepine, and lamotrigine). Based on the type of epilepsy, the patient's features, and the drug's qualities, the treating physician administered the necessary AED to the patient.

Using a patient particular sheet and data from the patient's seizure diary, the patient's specifics and details of the disease and medications were acquired at baseline, six weeks, and twelve weeks of follow up. Patients kept a seizure journal that they updated weekly, and this seizure diary was assessed at the halfway point and the final point of the follow-up period. At 0, 6, and 12 weeks of follow-up, patients had their adverse medication reactions evaluated. They were also evaluated for spontaneously reported adverse drug reactions at any point during the study.

Statistical analysis: Student's t-test and chi-square tests were applied. A p value of less than 0.05 was considered as statistically significant.

Results

The baseline demographic profile of patients in both the groups was comparable and is depicted in Table 1. The mean age of patients in group A and group B was 34.58±1.8 years and 30.02±1.62 respectively while median age was 27 years. Occupation wise, majority of the patients were employed in group A i.e., 50.7% while Group B had 47.6% patients as students. Considering education wise both the groups A and B had maximum patients who were educated more than 10th standard i.e., 60.35 and 79.3% respectively. The baseline clinical and epilepsy characteristics of the patients in both the groups A and B were comparable as depicted in Table 2.

Table 1 Demographic profiles of patients at the baseline

Characteristics	Group A	Group B
Total no. of patients	63	63
Age in years	34.58±1.8	30.02±1.62
Sex (M: F)	37:26	30:33
Occupation		
Employed	50.7%	28.5%
Housewives	22.2%	22.2%
Unemployed	1.5%	1.58%
Students	25.3%	47.6%
Education		
< 10th standard	39.6%	20.6%
>10th standard	60.3%	79.3%
Smokers	1.6%	1.6%
Alcoholics	15.9%	7.9%

Table 2 Clinical and epilepsy characteristics of the patients at baseline

Characteristics	Group A	Group B
Clinical Characteristics		
Pulse rate (Beat/minute)	79±8.2	80±6.3
Weight (Kilograms)	65.92±1.78	63.28±1.9
Blood pressure (mm of Hg)		
Systolic BP	114±1.9	113±1.7
Diastolic BP	72.6± 1.3	73±1.3
Newly diagnosed cases	68.3%	65.1%
Old diagnosed cases	31.7%	34.9%
Epilepsy Characteristics		
Generalised tonic-clonic	65.07%	55.5%
Partial	34.9%	36.5%
Unclassified	0%	55.5%
Mean duration of illness (years)	6.01±7.2	6.01±8.4
Mean duration of seizure episode (min)	2.5±0.19	2.3±0.14
Post ictal confusion	73%	66.7%
Status epilepticus	3.2%	7.9%
Positive family history	14.3%	12.7%

Values expressed as percentages and mean ± SE

The baseline pattern and characteristics of epilepsy such as type of seizure, mean duration of illness (in years), mean duration of seizure episode (in minutes), post-ictal confusion, status epilepticus and positive family history were comparable in both the groups A and B.

The Seizure characteristics including freedom from seizure, total number of seizures and time to first seizure are depicted in Table 3. The patients who achieved freedom from seizure did not vary significantly in both the groups A and B (p >0.5) As depicted in Table 4, in group A as well as group B, 21 (33.3%) patients each had freedom from seizure in 1st month of treatment. 14 (22.2%) patients in group A while 15 (23.8%) had freedom from seizures in 2nd month in group B. In 3rd month of treatment 8 (12.6%) patients in group A and 14 (22.2%) patients in group B had freedom from seizures. The number of patients who could not achieve freedom from seizure in group A was 20 (31.7%) and 13 (20.6%) in group B. The total number of seizures during the three-month treatment period. The total number of seizures did not vary significantly in both conventional and new AED groups (p>0.05).

The time to first seizure in both the groups i.e., group A and group B. In group A 25 (39.6%) patients had their first seizure in 1st month of treatment while in group B, 34 (53.9%) had first seizure in 1st month (p>0.05). Twenty (31.74%) patients experienced 1st seizure episode during second month of treatment whereas 10 (15.8%) patients in group B experienced 1st seizure in second month of treatment (p<0.05). In third month of treatment, 3 (4.76%) patients in group A while 4 (6.34%) patients in group B experienced their first seizure (p>0.05). 15 patients in each group did not experience seizures during the study period (p>0.05).

Table 3 Seizure characteristics in group A and group B

Seizure Characteristics	Group A	Group B
Freedom from Seizure		
1st month	21 (33.3%)	21 (33.3%)
2nd month	14 (22.2%)	15 (23.8%)
3rd month	8 (12.6%)	14 (22.2%)
No freedom	20 (31.7%)	13 (20.6%)
Total Number of Seizures		
0	15	15
1	24	24
4	15	10
3	4	4
4	1	6
5	2	1
6	1	0
7	1	2
11	0	1
Time to first seizure		
1st month	25(39.6%)	34(53.9%)
2nd month	20(31.74%)	10(15.8%)*
3rd month	3(4.76%)	4(6.34%)
No seizure	15(23.8%)	15(23.8%)

Values are expressed as percentages
**p value<0.05 as compared to group A*

The findings of the seizure diary maintained by the patient are depicted in Table 4. No patients in the study experienced seizures which came more often. The severity of seizures in terms of coming being same in severity did not vary significantly between the two groups (p>0.05). In terms of improvement in the severity of seizures also not a statistically significant difference was seen (p>0.05). Worsening of seizures or an emergence of a new type of seizure also did not vary significantly among the two groups (p>0.05). Also, there was no statistical difference in both groups regarding post ictal confusion (p>0.05), injury related to seizure (p>0.05), loss of consciousness (p>0.05), or presence of aura (p>0.05).

Table 4 Seizure diary findings in group A and group B

Parameter	1st month	2nd month	3rd month
More often			
@Group A	0	0	0
$Group B	0	0	0
Same			
Group A	24	20	16
Group B	23	10	12
Improving			
Group A	0	5	1
Group B	7	10	6
Worse			
Group A	2	5	3
Group B	2	6	3
New type			
Group A	1	1	0
Group B	1	1	0
Lasting longer			
Group A	2	7	5
Group B	2	4	0
Post ictal confusion			
Group A	7	9	7
Group B	1	0	0
Injury			
Group A	0	2	3
Group B	3	3	2
Loss of consciousness			
Group A	13	15	9
Group B	20	7	8
Aura			
Group A	1	6	3
Group B	3	1	1

*pvalue <0.05 as compared to group A
@ number of patients in group A=36
$ number of patients in group B=36

Table 5, shows the ADRs observed in both the groups A and B. The most common adverse drug reaction observed in patients in the group A was irritability which was reported by 33 (52.3%) patients followed by sleepiness which was observed in 31 (49.2%) patients out of the total of 63 patients. In the group B the most common ADR observed was again irritability observed in 30 (47.65%) followed by sleepiness seen in 21 (33.3%) patients out of total 63 patients. The ADR profile of both the drugs was similar except cognitive impairment, poor memory and swollen gums which were more common in the group A. The cognitive impairment as well as swelling of gums was seen with phenytoin. There was no serious adverse effect noted in any patients.

Table 5 Adverse drug reactions observed in group A and group B

Adverse drug reaction	Group A (n = 63)	Group B (n = 63)
Weight loss	9 (14.2%)	6 (9.5%)
Weight gain	18 (28.5%)	13 (20%)
Sleepiness	31 (49.2%)	21 (33.3%)
Tiredness	23 (36.5%)	15 (23.8%)
Irritability	33 (52.3%)	30 (47.6%)
Tremor	5 (7.9%)	2 (3.17%)
Rash	6 (9.5%)	2 (3.17%)
Concentration difficulty	23 (36.5%)	3 (4.7%)
Hair loss	13 (20%)	10 (15.8%)
Acne	6 (9.5%)	10 (15.8%)
Facial hair growth	0 (0%)	0 (0%)
Swollen gums	10 (15.8%)	1 (1.58%)
Poor memory	28 (44.4%)	10 (15.8%)
Slow speech	8 (12.6%)	0 (0%)
Headache	21 (33.3%)	13 (20%)

Discussion

Effectiveness of the conventional drugs and newer drugs are studied many a times but hardly generated some gross difference. The recent trend of choosing newer drugs is mostly due to the claim of better safety profile. In our study, the findings of the seizure diary suggested that the seizure severity did not vary significantly in the conventional and newer AED groups. Our findings are similar to another study where there was no difference in seizure severity [13]. Time to first seizure in both the groups i.e., the conventional and new AED group did not vary significantly between the two groups. The time to first seizure did not vary between the two groups in another study [14]. In contrast in another study the conventional group of drugs for the time to first seizure depicted better results than the newer group of drugs [15]. The seizure severity as well as time to first seizure was not expected to differ between the two groups as the effectiveness in controlling seizures of the AEDs in both the groups is well documented to be same.

In our study, the safety of patients was assessed by adverse drug reaction check list and by voluntary reporting for any adverse drug reaction during the entire study period. The adverse drug reactions did not vary between the two groups. This is in accordance with findings of a study which compared the conventional and newer AEDs and did not find a statistical difference in the adverse drug reactions [16].

In the present study, the most common adverse effect was irritability in both the conventional and newer AEDs followed by sleepiness. This is in accordance with findings from another study where irritability followed by sleepiness was the most common ADR encountered with antiepileptics [17]. In contrast another study done in India with antiepileptics demonstrated loss of appetite as the most common ADR encountered during the study [18].

There was a higher incidence of cognitive impairment and poor memory with the conventional AEDs as per the adverse drug reaction profile. This is in accordance with a number of studies which suggest that cognitive impairment is well documented with conventional AEDs [19]. In contrast another study suggested that cognition can be adversely affected by both conventional and newer AEDs [20]. In our study, the AED which caused maximal cognitive impairment was phenytoin. This finding is similar to a number of studies where phenytoin is associated with cognitive impairment [21,22]. Also swollen gums were more frequently seen in the conventional AED group. This finding is also well documented by the fact that conventional AEDs mainly phenytoin is implicated in gum hypertrophy [23]. There was no serious adverse effect noted in any patient. This finding is similar to another study [24,25]. Extensive literature search yielded only a few studies comparing effectiveness-safety of conventional and newer antiepileptic drugs in Indian population as well as globally. However, these studies have compared a few drugs only and not conventional and newer drugs as a group. Although, the study carries a limitation of washout period not being included, it was a step to provide a baseline data which will act as a scaffold for future studies to be built on.

Conclusion

In conclusion, our study found that newer AED have a comparable effectiveness yet they offer better safety profile as monotherapy for epilepsy. Hence, they can be considered as monotherapy in epileptic patients since they are required lifelong or long-term basis and safety of these medications is of prime importance.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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