Original Article APMC-344

Comparison of Efficacy of Sustained Release Formulation of Valproate and Topiramate Monotherapy for Control of Epilepsy in Epileptic Patients

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Submitted for Publication
01-11-2016
Accepted for Publication
22-11-2016

ABSTRACT

Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide. Medications are still the most common therapeutic choice for seizure control. In clinical practice anti-epileptic drugs that were licensed before valproate are called traditional antiepileptic drugs while those licensed after valproate are called new generation antiepileptic drugs. **Objective:** To compare the efficacy of sustained release formulation of valproate and topiramate monotherapy for control of epilepsy in elliptic patients. **Study design:** Randomized controlled trial. **Setting:** OPD, Medical Department, Allied hospital Faisalabad. **Duration of study:** 6 months duration after approval of synopsis from 30-07-2015 to 30-11-2015. **Methodology:** Patients with definite diagnosis of epilepsy with generalized tonic clonic seizures between 13 to 17 years of both genders were recruited from medical ward and OPD who fulfilled the inclusion were enrolled in the study. After approval from hospital ethical review committee. Informed consent was taken from each participant of the study. Patients were divided randomly into group A and group B using computer generated random number table. Group A was given sustained released formulation of valproate 500mg once a day and titrated up with weekly increments of 250mg/per day up to maximum of 2000mg/day in two divided doses to control seizures. Group B was given topiramate 25mg twice daily and titrated up in increments of 50 mg weekly to control seizures up to a maximum of 800 mg per day in 2 divided doses. Follow up was done by telephonic contact by asking about control of generalized tonic clonic seizures. Data was collected through self-conducted interviews using a standardized proforma. Efficacy was measured in terms of control of seizures. **Results:** In our study out of 330 cases, 165 in each group , 41.82%(n=69) in group-A and 40%(n=66) group-B were between 13-40 years of age while 58.18%(n=96) in group-A and 60%(n=99) in group-B were between 41-70 years of age ,mean was calculated as 41.79±10.66 and 42.12±10.37 years, 61.21%(n=101) in group-A and 54.55%(n=90) in group-B were male while 38.79%(n=64) in group-A and 45.45%(n=75) in group-B were females. Comparison of efficacy in both groups shows that 39.39%(n=65) in group-A AND 25.45%9(n=42) in group-B were treated effectively, p value was calculated as 0.006 showing a significant difference. **Conclusion:** We concluded that the efficacy of sustained release formulation of valproate is significantly higher when compared topiramate monotherapy for control of epilepsy in epileptic patients.

Keywords: Epilepsy, management, sustained release formulation of valproate, topiramate monotherapy, efficacy.

Article Citation: Hanif M, Hussain A, Shakoor S, Aamer M. Comparison of Efficacy of Sustained Release Formulation of Valproate and Topiramate Monotherapy for Control of Epilepsy in Epileptic Patients. APMC 2016;10(4):233-236.

INTRODUCTION

The term epilepsy denotes any disorder characterized by recurrent unprovoked seizures[1]. Epilepsy is one of the most common neurological disorders, affecting approximately 50 million people worldwide[2].

So far, Medications are still the most common therapeutic choice for seizure control. Anti-epileptic drugs that were licensed before valproate are called traditional antiepileptic drugs while those licensed

after valproate are called new generation antiepileptic drugs[3].

A number of new generation antiepileptic drugs(AEDs) have been registered over the past two decades[4]. The new generation AEDs have good pharmacokinetics and tolerability and demonstrate less potential risk for teratogenicity as compared to the traditional AEDs. It is believed that the new generation AEDs will replace traditional AEDs as first line choice for epilepsy.

International league against epilepsy (ILAE) proposed that choice of AEDs for epilepsy should be based on randomized control trials (RCTs).[5]

In one study by Hu Y et al, it was found that sustained release formulation of valproate achieved seizure control in 41.5% patient as compared to 28.3% with topiramate[6].

Recently many new generation AEDs have been registered with FDA and are being increasingly prescribed by clinicians. However, whether those new generation AEDs give rise to a better outcome remains unclear. Therefore, this stydy is carried out to compare the efficacy of the two most frequently used AEDS, the traditional antiepileptic drug of sustained release formulation of valproate (SRVPA) and the new generation antiepileptic drug "topiramate" with the aim to establish that, "the new generation AEDs are truly better than the traditional ones for epilepsy control".

METHODOLOGY

Sample technique:

Non probability consecutive sampling

Sample selection:

Inclusion criteria:

Age ranges from 13-70 years of both genders.

Patients with definite diagnosis of epilepsy with generalized tonic clonic seizures on basis of clinical history.

Exclusion criteria:

Pregnancy, lactating mother, febrile seizures, absence seizures, myoclonic seizures, atonic seizures and patients taking AEDs for migraine.

DATA COLLECTION PROCEDURE:

After approval from hospital ethical review committee. Informed consent was taken on the consent performa from each participant of the study. Patients were divided randomly into group A and group B using computer generated random number table. Group A was given sustained released formulation of valproate 500mg once a day and titrated up with weekly increments of 250mg/per day up to maximum of 2000mg/day in two divided doses to control seizures. Group B was given topiramate 25mg twice per day and titrated up in increments of 50 mg weekly to control seizures up to a maximum of 800 mg per day in 2 divided doses. Follow up was done by telephonic contact by asking about control of generalized tonic clonic seizures. Data was collected through self-conducted interviews using a standardized proforma. Efficacy was measured in terms of control of seizures.

STATISTICAL ANALYSIS:

All the collected information was transferred to SPSS version 20 and analyzed accordingly. Mean and standard deviation was calculated for all quantitative variables like age. Frequency and percentage were calculated for all qualitative variables like gender and efficacy. Chi square test was applied for efficacy. P value of <0.05 was considered as significant. Effective modifier like age and gender were controlled by stratification. Post-stratification chi-square test was applied.

RESULTS

In our study out of 330 cases, 165 in each group fulfilling the imclusion/exclusion criteria were enrolled to compare the efficacy of sustained release formulation of valproate and topiramate monotherapy for control of seizures in epileptic patients.

Age distribution of patients was done showing that 41.82%(n=69) in group-A and 40%(n=66) group-B were between 13-40 years of age while 58.18%(n=96) in group-A and 60%(n=99) in group-B were between 41-70 years of age ,mean was calculated as 41.79±10.66 and 42.12±10.37 years.(Table 1)

Table 1: Age distribution (n=130)

Age (in years)	Group-A (n=165)		Group-B(n=165)	
	No. of patients	%	No. of patients	%
13-40	69	41.82	66	40
41-70	96	58.18	99	60
Total	165	100	165	100
Mean±sd	41.79±10.66		42.12±10.37	

Patients were distributed according to their gender showing that 61.21%(n=101) in group-A and 54.55%(n=90) in group-B were male while 38.79%(n=64) in group-A and 45.45%(n=75) in group-B were females. (Table 2)

Table 2: Gender distribution (n=130)

Gender	Group-A (n=165)		Group-B (n=165)	
	No. of patients	%	No. of patients	%
Male	101	61.21	90	54.55
Female	64	38.79	75	45.45
Total	165	100	165	100

Comparison of efficacy in both groups shows that 39.39% (n=65) in group-A AND 25.45%9(n=42) in group-B were treated effectively while remaining 60.61%(n=100) in group-A and 74.55%(n=123) in group-B were not treated effectively, p value was calculated as 0.006 showing a significant difference (table no.3)

Table 3: Comparison of efficacy in both groups (n=130)

EFFICACY	Group-A (n=165)		Group-B (n=165)	
	No. of patients	%	No. of patients	%
Yes	65	39.39	42	25.45
No	100	60.61	123	74.55
Total	165	100	165	100

P=0.006

DISCUSSION

Epilepsy is one of the most common neurological disorders affecting 50 million people worldwide. Medications are still the most important therapeutic choice for seizure control. In clinical practice antileptic drugs used before valproate are called traditional antileptic drugs and after that the drugs called new generation antileptic drug. We planned the study to compare the efficacy of the two most frequently used antiepileptic drugs, the traditional drug of sustained release formulation of valproate (SRVPA) and the new generation antiepileptic drug topiramate with the aim to establish that, "the new generation antiepileptic drugs are truly better than the traditional ones for epilepsy control."

In our study out of 330 cases, 165 in each group , 41.82%(n=69) in group-A and 40%(n=66) group-B were between 13-40 years of age while 58.18%(n=96) in group-A and 60%(n=99) in group-B were between 41-70 years of age ,mean was calculated as 41.79+-10.66 and 42.12+-10.37 years, 61.21%(n=101) in group-A and 54.55%(n=90) in group-B were male while 38.79%(n=64) in group-A and 45.45%(n=75) in group-B were females. Comparison of efficacy in both groups shows that 39.39% (n=65) in group-A AND 25.45%9(n=42) in group-B were treated effectively, p value was calculated as 0.006 showing a significant difference. The findings of our study are supported with a study conducted by Hu Y et al, where it was recorded that sustained release formulation of valproate achieved seizure control in 41.5% patient as compared to 28.3% with topiramate[6].

Deleu D and others[7] evaluated the efficacy and safety of valproate (VPA) sustained released in monotherapy across all ages in newly diagnosed epileptic patients with partial seizures(PS) with or without secondary generalization they recorded that at 6 months, 87% of patients became seizure free with VPA sustained release monotherapy (average dose 22 mg/kg/day). Adverse drug reactions (hair loss and tremor) were recorded in 20% of patients, mostly affecting adults, they concluded that short-term treatment with VPA sustained release in monotherapy provides good seizure control and is well tolerated, this hypothesis support our findings.

Our study showed that topiramate had a higher failure than those on valproate, which was consistent with the results from the SANAD study (ARM b).[8]

However a double-blind randomized trial conducted by Privetera Md et al showed no difference in treatment failure between the two drug groups[9], which is contrary to our study. In this trial, the treatment dosage was fixed, and the period of follow-up was much shorter than that in our study, which could have led to the differences in outcome.

Yu PM and others[10] evaluated the efficacy, safety, and quality of life in patients using sustained release formulation of valproate. He concluded that patients receiving sustained release valproate as add-on or mono-therapy for 6 months exhibited significantly greater median percent reductions from baseline in seizure frequency for all seizure types and significantly higher response rates and higher

seizures freedom rates, with good tolerance and improved quality of life. This study also supports our results.

CONCLUSION

We conclude that the efficacy of sustained formulation of valproate is significantly higher when compared topiramate monotherapy for control of epilepsy in epileptic patients.

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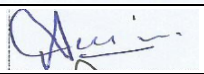
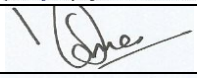
AUTHORSHIP AND CONTRIBUTION DECLARATION

Name of Author	Contribution to the paper	Author's Signatures
Dr. Muhammad Hanif	Tabulation of results, Proof reading Collection of data, Proof reading	
Dr. Aamir Hussain	Authentication of references, Proof reading	
Dr. Salman Shakoor	Study designing, Writing the manuscript	
Dr. Muhammad Aamer	Data analysis, Literature review, Proof reading Collection of data,