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A Clinic Based Comparative Study on Monotherapy and Combination Therapy in Epilepsy

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Abstract
The study was to evaluate and compare the effectiveness of single antiepileptic drugs with combination antiepileptic drugs in Idiopathic epilepsy in a routine clinical practice. Patients diagnosed with Idiopathic epilepsy and prescribed with a single antiepileptic drug and combinations of two antiepileptic drugs were included in the study. Out of 214 epilepsy patients, 8 patients were excluded for non-compliance and insufficient data. Patients were followed up for every 1-3 months in their outpatient clinic. Seizure activity was categorized into seizure freedom, reduction in seizure frequency and no change after therapy. We analyzed the effect of monotherapy and combination therapy on seizure frequency in patients with epilepsy (N = 206). 62 patients were on four different single antiepileptic drug and of them 32 were seizure free. 144 patients were on six different combinations of antiepileptic drugs and of them 87 were seizure free. We found the proportion of seizure-free cases with combination therapy was relatively less with monotherapy. We also found that the valproic acid (40.6%) had better outcome and a combination of levetiracetam with valproic acid (33.3%) had superior outcome measured against other AED combinations, concluding the suggestion for the use of combination therapy if initial monotherapy is unsuitable for the patients.

Keywords: *Seizures, Anti-epileptic drugs, Monotherapy, Combination therapy.*

Introduction

Epilepsy affects 50 million people worldwide.[1] The economic burden of neurological diseases is high all over the world. Epilepsy itself contributes 37 billion dollars annually in the United States[2]. With a conservative estimate of 1% as prevalence of epilepsy, there are more than 12 million patients with epilepsy in India, which accounts for nearly one-sixth of the global burden.[3] Seizures are typically classified as generalized, with synchronized cortical manifestation in both hemispheres, or partial, with focal cortical onset[4]. Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. More than 20 anti-epileptic drugs (AEDs) are now available, creating considerable challenges for physicians in choosing among drugs that synergistically control seizures while minimizing adverse effects.[5] Seizure-free outcomes are attained in 60% to 70% of patients with initial

monotherapy.[4,6] Treatment options for 30% to 40% patients include other AED combination therapy using an additional AED as adjunctive therapy. Data from AED combination therapy trials in patients with POS have shown elimination of seizures in 15% to 35% of patients and reduction of seizure frequency by more than half in 12% to 29% of patients.[5] Choosing the correct or better AED may provide early relief, alleviate or reduce adverse effects, improve prognosis, and reduce financial burden in affected patients.[7] If the first AED monotherapy is ineffective, adding a second AED, then tapering and discontinuing the ineffective AED, is the preferred approach. If the second sequential AED monotherapy is ineffective, an adjunctive AED with a different and potentially complementary MOA should be considered for use in adjunctive polytherapy.[8] Polytherapy is more expensive than monotherapy. Furthermore, patients may find it more difficult to manage and comply with polytherapy than with monotherapy, which in turn may lead to failure to control seizures. Although polytherapy is prescribed when monotherapy fails to control seizures. Unfortunately, there have been insufficient clinical trials to determine the best combinations of AEDs.[9] Our study analyzed the effects of single AED and combination AED, also to show the possible better combination AED prescribed in a private clinical hospital.

Methodology

Study criteria

Patients diagnosed with epilepsy and prescribed with a single antiepileptic drug and combinations of two antiepileptic drugs were included in the study. Patients with chronic illness or other co-morbid condition like hypertension, metabolic syndrome, renal disorders, any progressive CNS diseases, psychiatric condition, trauma prior to epilepsy and with polytherapy and chronic medications other than AEDs were excluded from the study. Out of 214 epilepsy patients, 8 patients were excluded for non-compliance and insufficient data.

Registry setup

This study was a prospective, observational study of epileptic patients in a routine clinical practice carried out between January 2015 and September 2017. The study was approved by the Institutional Ethics Committee and all the patients consent was obtained. The data regarding patient's demographics, age of onset, clinical manifestations, number of seizures one year before medication, medication history about previous antiepileptic treatment, co-morbidities (cerebral trauma, brain tumor, cerebrovascular disorders, developmental anomalies of cerebral structure) and other related neurologic conditions, general physical examination results, and neurological examination results. Results of laboratory examinations, imaging examinations (computed tomography [CT], magnetic resonance imaging [MRI] and electroencephalogram (EEG). Patients were followed up (as outpatients) every 1–3 months. Seizures (if any) were recorded in diaries by patients or their families and provided to the physician. Prognosis and treatment effectiveness was updated in the follow-up visits. If the patients did not visit the outpatient clinic over 6 months period, we tried to contact them over phone and recorded the data. It was provided through paper-based case report form, computerized for cross check the results through data sheet.

The therapeutic activity was categorized into three main outcomes (i) seizure freedom, with no seizure activity in the past twelve months; (ii) reduce in seizure activity, reduction in seizure episodes with no change in frequency, (iii) no change. In addition, alternative treatment or the ongoing drug doses were tapered accordingly to the patient needs and response.

Results

A total of 214 epilepsy patients (male/female: 133/81; 62% males, 38% females; aged 4-30 years) on single AED (n=62) and combination AED (n=144) were included the study. The most common epilepsy type was Idiopathic epilepsy

(n=121; 58.7%), Generalized tonic-clonic epilepsy (n=46; 22.3%), complex partial seizures (n=20; 9.7%), atypical febrile seizures (n=14; 6.7%), juvenile myoclonic seizures (n=13; 6.3%) as seen in Table 1. Under monotherapy 4 different AEDs were prescribed, twenty-seven patients (43.5%) were on levetiracetam [LEV], twenty-two (35.4%) patients were on valproic acid [VPA], ten (16%) on oxcarbazepine [OXC] and three (4.8%) on phenytoin [PHE]. Seizure freedom was reported in thirty-two (51.6%) patients with monotherapy. A combination of 6 AEDs were prescribed, forty-five patients (31.2%) were on levetiracetam and clobazam, forty two (29%) patients on levetiracetam and valproic acid [LEV+VPA], eighteen patients (12.5%) on valproic acid and clobazam [VPA+CLB], fifteen (10.4%) on levetiracetam and oxcarbazepine [LEV+OXC], twelve patients (8.3%) on valproic acid and lamotrigine [VPA+LTG], phenytoin and clobazam [PHE+CLB] respectively as shown in Table 2. Seizure freedom was achieved in 87 patients (60.4%). In our study, the individual agent with more seizure-free outcome was observed with valproic acid (40%) followed by levetiracetam (37.5%). Whereas, in combination therapy it was LEV+VPA (33.3%) followed by LEV+CLB (31%). The results are shown Figure 1.

Table 1 Epileptic characterization and type of treatment in patients

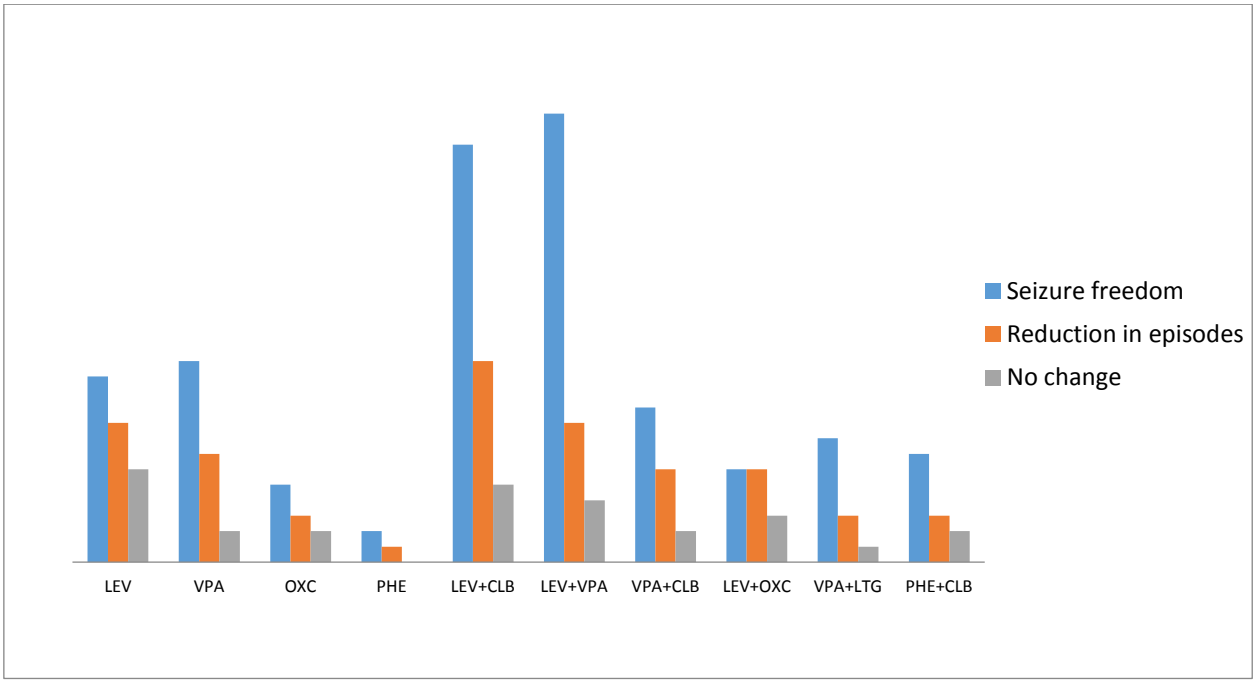
Types of epilepsy	**Number of patients (percentage)**
Number of patients	206
Males	133 (62%)
Females	81 (38%)
Neurological diagnosis	
Idiopathic epilepsy	121 (58.7%)
Generalized tonic-clonic epilepsy	46 (22.3%)
Complex partial seizures	20 (9.7%)
Atypical febrile seizures	14 (6.7%)
Juvenile myoclonic seizures	13 (6.3%)
Type of therapy	
Monotherapy	62 (30%)
Combination therapy	144 (70%)

Table 2 Patients exposed to single AED and combination AED

Monotherapy and Combination therapy	**Number of patients (percentage)**
LEV	27 (43.5%)
VPA	22(35.4%)
OXC	10 (16%)
PHE	3 (4.8%)
LEV+CLB	44 (31.2%)
LEV+VPA	42 (29%)
VPA+CLB	18 (12.5%)
LEV+OXC	15 (10.4%)
VPA+LTG	12 (8.3%)
PHE+CLB	12 (8.3%)

LEV==Levetiracetam; VPA=Valproic acid; OXC=Oxcarbazepine; PHE=Phenytoin; LTG=Lamotrigine; CLB=Clobazam

Figure 1: Therapeutic outcomes of single and combination AED



LEV=Levetiracetam; VPA=Valproic acid; OXC=Oxcarbazepine; PHE=Phenytoin; CLB=Clobazam; LTG=Lamotrigine.

Discussion

The initial monotherapy is the standard treatment for patients with newly diagnosed epilepsy. If the initial monotherapy fails to control seizures adding alternative AED is recommended. Even though the drug fails to manage seizures, combination therapy is suggested.[9,10] The results of the study indicate that both monotherapy and combination therapy shows relatively similar therapeutic outcome. The proportion of seizure freedom outcomes was less between VPA, LEV and LEV+CLB, LEV+VPA. This study helps to confirm previous clinical data suggesting the use of various AEDs in epileptic patients.

Korby et al,[11] Daria stepanova et al,[12] Depondt et al,[13] Ji Hyun Kim[14] stated that levetiracetam was more efficacious and resulted in more seizure-free outcomes and Unsal Yilmaz et al[15] with oxcarbazepine. Valproic acid had a better responder rate and seizure free outcome in our study. Daria stepanova et al[12] states that levetiracetam with clobazam, P.D. Knoester,[16] Nicholas P. Poolos,[17], Jukka Peltola[18] stated that valproic acid with lamotrigine had shown superior efficacy compared with other AED. In another study with clobazam add-on therapy with levetiracetam, valproic acid had more seizure-free outcomes.[19] Levetiracetam and valproic acid were reported with more seizure free outcomes in our study. This could be a new AED combination. When drugs are combined, a risk of both pharmacokinetic and pharmacodynamic interactions exists. At present it is common clinical practice to add AEDs for unresponsive patients even few are maintained on two, three, or even four AEDs. This is so because the newer AEDs do not cause more side effects.[20] Selection of AED combinations by mechanism of action may be useful because AEDs with similar mechanisms may have similar side effect profiles. A combination of AEDs with distinct mechanisms may produce different efficacies by their synergistic action and reduces the incidence of side effects.[5]

Conclusion

The initial monotherapy is the first choice for newly diagnosed epilepsy patients. Combination therapy is preferred when patient is unresponsive to monotherapy. As different AEDs are available

in the market, a physician must consider appropriate AED with less toxicity and better tolerability. Our study found that treatment with valproic acid and valproic acid with levetiracetam has shown better outcomes than other anti-epileptic drugs in the study.

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