New Versus Classic Antiepileptic Drug Therapy In Pediatric Epilepsy

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Abstract: The current study was designed to compare the efficacy and safety between new and classic antiepileptic drugs (AEDs). Children diagnosed with epilepsy from birth to 12 years old were included in the present study. All data were collected retrospectively and twenty six children were enrolled in the analysis. Predominant seizure types were generalized tonic-clonic and the classical drugs were the most commonly prescribed drugs. Five patients (19%) among those who were treated with classic drugs become seizure free compared to 1 patient only (4%) who became seizure free from those who were treated with new antiepileptics. No side effects were reported except for 2 patients receiving the classic drug, carbamazepine, who developed skin rashes and dizziness. In conclusion, the results of the current study showed that the classic AEDs remain essential and still considered as the first line treatment in pediatric epilepsy.

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1. Introduction:

Epilepsy is one of the classicist neurological conditions and is the most frequent neurodegenerative disease after stroke [1]**.** Approximately 10% of people in the United States will suffer a seizure, with 1% to 3% developing epilepsy. The annual incidence of epilepsy is about 50 per 100,000 with a prevalence of 5–10 per 1,000 [2]**.** In a previous study done by Al Rajeh et al. 2001, the prevalence of epilepsy in Saudi Arabia was 6.54=1000 population, where 28% was partial seizures, 21% was generalized seizures and 51% was also generalized seizures but without determination if that seizures had focal onset or not [3].

With drug treatment, 50% of the patients with epilepsy are completely controlled with drug treatment, while the frequency of seizures is reduced in 25% [4]. Over the past two decades, several new antiepileptic drugs (AEDs) have been developed and introduced to the market with the global aim of providing a better control of the seizures and a more favorable safety and tolerability over the so-called classic AEDs [5]. Starting from 1991, newer AEDs including lamotrigine, gabapentin, oxcarbazepine and pregabalin, have been developed and marketed primarily as add-on therapy in patients with epilepsy whom seizure fits were not well controlled by classical AEDs. However, newer AEDs are currently approved to treat epilepsy also as monotherapy [6]

The number of drugs used to treat pediatric epilepsy has increased dramatically in the last decade due to development of new AEDs. Recently and since their approval, the prescription of the new AEDs have been increased whereas the classic AEDs as phenytoin and carbamazepine have been decreased [7]**.** The aim of the present study was to investigate the antiepileptic drug therapy in pediatrics and compare the efficacy and safety between classic and new antiepileptic drugs in Jeddah, Saudi Arabia.

2. Patients and methods

A retrospective chart review was performed at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia on children, from birth to 12 years, diagnosed with epilepsy based on clinical evaluation and electroencephalogram (EEG) abnormalities, who were treated with antiepileptic drugs from 2000 to 2012. The study was done after approval from KAUH review board and it was conducted to assess the efficacy and tolerability of antiepileptic drugs in children.

All children with developmental delay, brain malformations, and inborn errors of metabolism were excluded from the study. Data were collected retrospectively regarding age, gender, seizure type, regimen (mono or multiple therapy), whether the patients improved or not, adverse effects and comorbid conditions .

Thirty eight children who met the diagnostic criteria were enrolled. Among these children, 12 patients were excluded from the analysis: 8 patients had insufficient information regarding the treatment, and 4 patients were lost to follow-up. The data were collected randomly by computerized system. Drugs for acute use were excluded from the study.

3. Results

Twenty six children (14 boys and 12 girls) were enrolled in the analysis of the current study (Table 1). The average age of the onset of the seizure type was found to be from birth to 12 years (mean = 3 years). The present study showed that the predominant seizure types were generalized tonic clonic 18 (69%) and myoclonic seizures 4 (15%). Other seizure types were febrile seizure 1 (4%), partial seizure 1 (4%), jerky movement 1 (4%) and right focal epilepsy 1 (4%). The mean duration of treatment was 5.25 years.

The current study revealed that the classical drugs were the most commonly prescribed drugs (58%) mainly carbamazepine, valproate and phenobarbital, whereas the prescribed newly antiepileptic drugs were 12% including mainly lamotrigine, levetiracetam and topiramate. However combination treatment was found in 31% of the children (Figure 1).

The data analysis of the present study revealed that 5 patients (19%) among those who were treated with classic drugs become seizure free compared to 1 patient only (4%) who became seizure free from those who were treated with new antiepileptics. Improvement in seizure frequency was observed in 10 (39%) of patient receiving classic agents, 2 (8%) receiving new agents and 6 (23%) using a combination of classic and new antiepileptic drugs. Only 2 patients (8%) of the 26 showed no improvement while using combination therapy (Figure 2). No side effects were reported except for 2 patients receiving the classic drug, carbamazepine, who developed skin rashes and dizziness.

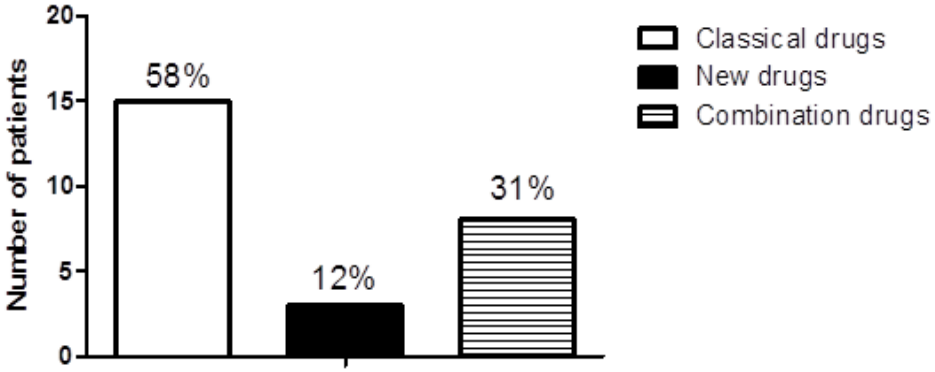

Figure 1. Comparison between the number of patients using classical, new and combination therapy

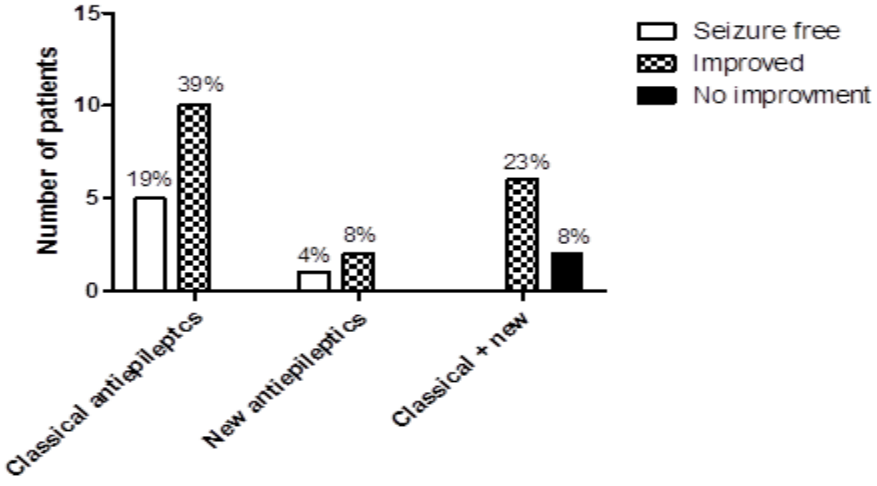

Figure 2. The outcomes of classical, new and combination antiepileptic therapy

Table 1. Patient data for children with epilepsy who received classic and new antiepileptic drugs

ID	Age/ sex	Types of seizure	Duration of treatment	Mono or multi	Drugs used	Dose	Improvement	Side effects
1	7yrs/M	Tonic clonic	1 yr	Mono	Valproate	5ml tid	Improved EEG, MRI	None
2	10yrs/M	Generalized tonic clonic	2yrs	Mono	Valproate	5ml bid	Improved EEG (mild attacks)	None
3	3yrs/M	Febrile seizure	5yrs	Mono	Carbamazepine	7.5mg bid	Improved EEG	none
4	7yrs/M	Tonic clonic	6 mon	Mono	Carbamazepine	300mg	Improved clinically	none
5	3d/M	myoclonic	1yr	Multi	Valproate Lamotrigine Leviteracetam	4ml bid 75mg bid 125mg od	Improved clinically , EEG	None
6	4yrs/F	partial	3yrs 9 mon	Mono	Carbamazepine	100 mg po bid	Cured EEG	None
7	4mon/M	Tonic clonic	4 mon	Multi	Topiramate phenobarbital	25mg od po 30mg od po	Free 1.5 mon clinically	None
8	2days/M	Generalized tonic clonic	3yrs	Mono	Carbamazepine	2.5ml tid	Cured clinically	None
9	5mon/M	Generalized tonic clonic	6 yrs	Multi	Levitricetam Topiramate	12.5mg po bid	Cured clinically	None
10	4yrs /F	Tonic clonic	3yrs 8 mon	Mono	Valproate	200mg bid	Improved clinically	None
11	2yrs/M	Tonic clonic	2yrs	Mono	Valproate	100mg bid	Cured EEG	None
12	4yrs/F	Febrile Tonic clonic	1yr	Mono	Carbamazepine	600mg/d	Cured clinically	none
13	6yrs/F	Febrile Tonic clonic	2yrs	Mono	Carbamazepine	600mg/d	Cured clinically	None
14	3d/F	Jerky movement	2yrs	Mono	Carbamazepine	7ml bid	Improved clinically	None
15	5yrs/M	Febrile Tonic clonic	4mon	Mono	Phenobarbital	2ml bid	Improved clinically	None
16	5yrs/F	Tonic clonic	3yrs	multi	Carbamazepine Topiramate	100mg 250mg	Improved clinically	None
17	2yr/F	myoclonic	6mon	Multi	Valproate Topiramate	15omg 25mg	Improved clinically	None
18	2yr/M	Tonic clonic	2yrs	Multi	Carbamazepine Topiramate	100mg 25/50mg	Still have attacks	None
19	5yrs/F	right side focal epilepsy	1yrs, 1mon	Multiple	Carbamazepine leviteracetam	4.8mg/kg/d 400mg bid	Improved EEG	None
20	3yrs/F	Generalized tonic clonic	1.5 yr	Multi	Valproate Topiramate	175mg bid 25 mg bid	Improved Weaning valproate	None
21	4yrs/M	Myoclonic	1yr	Multi	Valproate Lamotrigin	750mg 200/160 mg	Not improved	None
22	6d/M	Myoclonic	1yr	Mono	Carbamazepine	50mg bid	Improved CT scan	Skin rash
23	8yrs/M	Tonic clonic	6yrs	Mono	Carbamazepine	200/ 400 mg	improved EEG	dizzness
24	1mon/F	Tonic clonic	1yr	Multi	Topiramate Levetiracetam	25mg bid 500 mg	Improved clinically	None
25	2yrs/F	Tonic clonic	4yrs	Mono	Valproate	20 mg/kg/d	Improved EEG	None
26	10days/F	Generalized tonic clonic	2yrs	Mono	Levetiracetam	600 mg po bid	Improved clinically & CT scan	None

4. Discussion

Epilepsy is one of the most frequent chronic neurologic disorders and long-term AED treatment is required in many patients [8]. In the past two decades, the development of new AEDs aimed to improve the effectiveness and reduce the adverse effects of drug therapy [9]. Regarding the effectiveness, "classic" and "newer" AEDs have been reported to have comparable efficacy. On the other hand, the newer AEDs have been showed to have fewer adverse effects than classic ones. However, knowledge about potential long-term effects of the "newer" AEDs is limited [10, 11, 12, 13]

The results of the present study showed the relevant differences in the trend of prescribing and use of classic and new AEDs. Thus far, only a few studies have showed how the initiation and development of the new AEDs changed the prescribing patterns in pediatric epilepsy. The International League Against Epilepsy (ILAE) recommends classic AEDs as first-line treatment in the management of most pediatric seizures while the new AEDs are mainly recommended as a second-line option. Moreover, the daily costs of the new AEDs can be almost three times as high as the costs of classic AEDs, which may affect the physician prescribing pattern [14]

In the present study, the classic AEDs were prescribed more frequently and were almost four times as much as the new ones. This finding was in accordance with the results of a previous study by Hsia et al [15] which revealed that classic AEDs were found to be the main treatment choice in pediatric epilepsy in the United Kingdom, Italy and the Netherlands from 2001 to 2005. Moreover, older AEDs were found mostly prescribed for epileptic disorders in Italy [16].

For patients on new AEDs "regardless whether they were receiving mono or polytherapy" lower improvement was reported. The Improvement was higher in patients on classic AEDs (58%) than those on new AEDs (12%). While the combined treatment between classic and new AEDs showed fewer efficacies than classic AEDs (31%). Also the prevalence of use of classic AEDs was higher than newer AEDs.

The results of study done by Asconape [17] showed that the newer AEDs showed no better efficacies than the classic ones but they are easier to use with much better pharmacokinetic profiles and fewer drug-drug interactions. Perucca and colleagues, [18] found that there was no difference in the efficacy between classic and new AEDs in patients with newly diagnosed epilepsy but some of newer drugs offer advantages in terms of improved tolerability, ease of use, and reduced interaction potential.

On the other hand, Sendrowski [19] found that the new AEDs are better tolerated, have fewer drug interactions and seem to affect cognitive functions to a lesser degree compared to the conventional drugs. Moreover, the study done by LaRoche [20] and colleagues showed that new antiepileptic drugs offer many options in the treatment of epilepsy, each with a unique mechanism of action as well as an adverse effect profile. The new AEDs are well tolerated with few adverse effects, minimal drug interactions, and a broad spectrum of activity.

The main limitation of the present study was that it was a retrospective study depending on the files of the patients without direct contact with them with its subsequent drawbacks as loss of follow up for some patients, some missing data, lack of documentation and lack of availability of some AEDs (e.g.: ethosuximide was not present in the formulary at KAUH, so the absence seizure was excluded and not discussed in the current study).

Conclusion

In conclusion, the results of the current study showed that the conventional classic AEDs remain essential and still considered as the first line treatment for childhood epilepsy.

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