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Comparison of Levetiracetam With Sodium Valproate in Controlling Seizure in Patients Suffering From Juvenile Myoclonic Epilepsy

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Background: Juvenile myoclonic epilepsy is the most common type of generalized idiopathic epilepsy. Sodium valproate is the first line of medications, but has many complications and 15% of patients are resistant to this medicine. This is a lifelong disease and in case of stopping the medication, relapsing of seizures is seen in more than 80% of cases.
Objectives: Analysis the effectiveness of these two drugs on controlling patients seizures by comparing them in mono therapy treatment of JME and to represent levetiracetam as a replacement of sodium valproate for first line medication of JME.
Patients and Methods: In this study we compared the effectiveness of sodium valproate and levetiracetam for 66 patients having juvenile myoclonic epilepsy and followed them for 6 months.
Results: Comparison of mean generalized tonic colonic attacks in two groups with didn't show meaningful differences (P = 0.95), also, by comparing the mean of myoclonus attacks in patients of two groups before starting study, no meaningful difference was gained (P = 0.71).
Conclusions: It became clear at the end of the study that the effectiveness of two drugs were the same and they didn't have any meaningful difference. According to the result gained from this study, levetiracetam is a proper alternative treatment instead of sodium valproate which has appropriate effectiveness along with lower complications.

Keywords: Levetiracetam; Sodium Valproate; Juvenile Myoclonic Epilepsy

1. Background

Juvenile myoclonic epilepsy (JME) is the most common type of generalized idiopathic epilepsy, and consist 5 - 11% of all epilepsies. This disease can cause three types of seizures: myoclonic jerks, generalized tonic colonic seizures (GTC) and absence attacks. Myoclonic seizure is seen in all of the patients, generalized tonic colonic seizure in 90% of the them and absence appear in one third of the patients.

Imaging finding of brain are normal. The octal electro encephalogram (EEG) shows generalized spike and poly spikes of 3-6Hz (1). A lifelong medication for this disease is necessary. Seizures will relapse by stopping the treatment in 80% of cases (2). Sodium valproate is the first line of medication for JME. According to the researches, in 41-88% of patients seizures were completely controlled by taking sodium valproate (3). 15% of JME patients are resistant to treatment with sodium valproate, and some patients cannot tolerate the complication of this drug such as, hair loss, weight gain, tremor and menstrual disorders (4).

Other drugs which can be used in treatment of JME are: levetiracetam, topiramate, zonisamide and lamotrigine (5, 6). There are reports supporting the effectiveness of levetiracetam in JME patients resistant to medication by sodium valproate and lamotrigine and seizures of 50% of patients were completely controlled by treatment of levetiracetam (4). Levetiracetam has lower complications and is tolerable even in high doses (7). On the other hand, taking sodium valproate during pregnancy is accompanied with highest risk of fetal malformations (10.7%) while taking levetiracetam during pregnancy doesn't increase the risk of fetal malformations (8). Noticing the complications of sodium valproate, increase in the risk of fetal malformation and resistance of some patients to this treatment, and on the other hand, the lower complications of levetiracetam and its safety on pregnancy.

2. Objectives

We aimed to analyze the effectiveness of these two drugs on controlling patients seizures by comparing them in mono therapy treatment of JME and to represent levetiracetam as a replacement of sodium valproate for first line medication of JME.

3. Patients and Methods

Juvenile myoclonic epileptic patients were chosen from

referrals to neurology clinic of Golestan hospital in Ahvaz after being neurologically and systemically examined, by standards revealed by International League Against Epilepsy. Providing the existence of secondary cause for epilepsy, requiring more than one anti-epileptic drug, severe organic disease, electrolytic and metabolic disorders, pregnancy, history of using alcohol or drug dependency, patients were excluded from research.

Randomly, patients were taken under treatment of levetiracetam or sodium valproate. At first level, tests of CBC and renal and liver function were taken which in case of having an important disorder (based on exclusion criteria) patients was eliminated from the research. Latter tests were repeated at the end of 4th, 12th and 24th weak and patients were ruled out of research if having an significant disorder.

At the second level (dose escalation period), which lasted for 4 weeks, levetiracetam (levebel of cobel darou company) was started in one group with the dosage of 250 mg two times a day and the dosage was increased after one week. In case of not having controlled seizures, dosage was increased weekly till the time which seizures become under control, or drug complications appear, or the drug reaches its full dosage of 3000 mg per day.

In other group, sodium valproate (Depakin of Sanofi Company) was started with the dosage of 500 mg daily and the dosage was increased after one week. In case of not having controlled seizures, dosage was increased weekly till the time which seizures become under control, or drug complications appear, or the drug reaches its full dosage of 3000 mg per day.

At third level, (maintenance phase), final dosage of each drug was contained for 20 weeks. Before starting the treatment, drug complications were warned to the patients, to call the physician researcher in case of their incidence. Patients were excluded of research and got proper treatment in case of drug resistance or not having seizures under control.

After 24 weeks of treatment, the frequency of seizures were recorded based on number of attacks during a month. So by comparing the frequency of seizures before and after the treatment in the two groups, the result was analyzed for each group and the effectiveness of these two drugs was compared to each other.

4. Results

From 69 persons of participants in the study, 2 persons from sodium valproate group due to intolerance of drug and one person from levetiracetam group for not willing to take the drug were excluded of the research and eventually, 34 persons remained in sodium valproate group and 32 persons in levetiracetam group. The elimination of mentioned patients didn't have influence on statistical result of the research.

Table 1 shows the demographic specifications of participants of this study. Comparison of two groups by gender (P value = 0.12) and mean of age (P value = 0.92) didn't show meaningful difference. As it is obvious, taking sodium valproate was accompanied with meaningful difference (decrease) in mean incidence of GTC and myoclonus in this research.

Taking levetiracetam was accompanied with meaningful difference (decrease) in mean incidence of GTC and myoclonus in this study (Tables 2 and 5). There wasn't any meaningful difference in the mean GTC and myoclonus frequency at the beginning of study between two groups taking sodium valproate and levetiracetam in independent t-test. There wasn't any meaningful difference in the mean GTC and myoclonus frequency at the end of study between two groups taking sodium valproate and levetiracetam in independent t-test (Tables 4 and 5).

Table 1. Demographic Specification of Participants in This Study [a]

Drug Group	Sodium Valproate	Levetiracetam
Gender		
Male	10 (29.41)	9 (28.12)
Female	24 (70.58)	23 (68.75)
Total No.	34	32

[a] data are presented as No. (%).

Table 2. Relative Abundance of Variety of Seizures in Each Groups Before Starting the Study and at the End (After 6 Months) [a]

Drug Group	Sodium Valproate	Levetiracetam
Patients with myoclonus		
At the beginning	100	100
At the end	23.5	28.1
Patients with GTC		
At the beginning	91.17	87.5
At the end	14.7	15.62

[a] data are presented as percentage.

Table 3. Mean of Frequency of GTC and Myoclonus Monthly Before and After the Treatment (After 6 Months) [a]

Drug group	GTC Before Treatment	Myoclonus Before Treatment	GTC After Treatment	Myoclonus Before Treatment
Sodium valproate	1.26 ± 0.96	3.67 ± 1.88	0.26 ± 0.44	1.21 ± 0.97
Levetiracetam	1.25 ± 0.98	3.75 ± 1.89	0.25 ± 0.43	1.02 ± 1.24

[a] Data are presented as Mean ± SD.

Table 4. Paired t-test for Evaluation of Difference Between Mean of GTC and Myoclonus Attacks Before and After the Treatment in the Sodium Valproate and Levetiracetam Taking Groups

Groups	Differences [a]	P Value
Valproate group		
GTC (before and after treatment)	1 ± 0.11	0.0001
Myoclonus (before and after treatment)	2.73 ± 0.21	0.000
Levetiracetam group		
GTC (before and after treatment)	1 ± 0.71	0.000
Myoclonus (before and after treatment)	2.73 ± 1.21	0.000

[a] Data are presented as Mean ± SD.

Table 5. Comparing the Difference of Mean GTC and Myoclonus Frequency in Two Groups Taking Sodium Valproate and Levetiracetam: at the Beginning and End of Study

Groups	Mean Differences	P Value
GTC, end of study	1.73	0.71
GTC, beginning of study	0.094	0.95
Myoclonus, end of study	1.68	0.78
Myoclonus, beginning of study	0.05	0.83

5. Discussion

Juvenile myoclonic epilepsy is the most common type of generalized idiopathic epilepsy specially in women (1). There is a necessity for lifelong treatment for this disease and seizures relapse in more than 80% of cases, by stopping the treatment (2).

Sodium valproate is the first line of medication of these seizures with effectiveness of 41 - 88% (3). In case of sodium valproate intolerance or not having proper response, lamotrigine, topiramate, zonisamide or levetiracetam can be used (5) levetiracetam may be the best new drug against seizures in treatment of juvenile myoclonic epilepsy, and noticing the fact that it's well tolerated and has few complications, it can be the alternative of sodium valproate in treatment of this disease (3).

In this research, for patients being under treatment of sodium valproate, after 6 months of follow, 83.87% of generalized tonic colonic seizures and 76.5% of myoclonus cases were controlled. In patients under treatment of levetiracetam, 87.5% of generalized tonic colonic seizures and 71.9% of myoclonus cases were controlled.

The mean GTC seizure attacks of patients was 1.26 for the group taking sodium valproate and 1.25 for the levetiracitam group. Comparison of mean GTC attacks in two groups with ANOVA test didn't show meaningful differences (P = 0.95). Also, by comparing the mean of myoclonus attacks in patients of two groups before starting research, no meaningful difference was gained (P = 0.71).

In Schape study, levetiracetam was prescribed for 30 JME patients and seizures were controlled in 80% of patients after follow up of 6 months and in 96.6% after 12 months (3). It was seen in another research that, levetiracetam controlled 53.8% of myoclonus and 80% of generalized tonic colonic seizures (9). It was observed in another research that in 80% of patients taking levetiracetam seizures were completely controlled (10).

It became clear from our research that both sodium valproate and levetiracetam drugs had meaningful effects on reducing the mean GTC attacks after 6 months (P = 0.0001 and 0.000 respectively). The effectiveness of the two drugs on reducing the mean myoclonus attacks was also meaningful. (P = 0.000 for sodium valproate and levetiracetam).

By comparing effect of the two drugs on GTC attacks there wasn't any meaningful difference in mean of GTC attacks between sodium valproate and levetiracetam groups at the end of research (P = 0.95) also, the comparison of mean myoclonus attacks in two drug groups at the end of research, didn't show any advantage of sodium valproate on levetiracetam (P = 0.78). In fact, in this research, no priority was seen between sodium valproate and levetiracetam drugs in reducing GTC and myoclonus attacks in patients having juvenile myoclonic epilepsy. No noticeable drug complication was seen in participants of the research during the study.

According to the gained results, levetiracetam is an appropriate drug for treatment of JME, which has similar effectiveness of sodium valproate but not having its complications. This research supports the prescription of levetiracetam as first line medication of JME. For more accurate observations, studying with bigger sample size and longer follow up time is suggested.

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