ORIGINAL ARTICLE

Does levetircetam decrease of the rubral tremor in patients with multiple sclerosis

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Background: One of the frequent symptoms of Multiple Sclerosis (MS) is tremor which can severely cause disability. Treatment of tremor in MS patients is still very challenging to manage. In this study, we sought to determine the efficacy of Levetiracetam on treatment of MS-related tremor. **Materials and Methods:** This clinical trial study was conducted among 22 patients from July 2012 to April 2012 in Alzahra-Hospital, Isfahan, Iran. Patients were given 500 mg Levetiracetam twice a day for 1 week. The drug dosage increased 1000 mg per week until reaching the peak dose of 50 mg/kg. After a 2 week period of washout, first phase was repeated. The subjects were assessed at baseline, after first intervention, after wash-out period, and after second intervention. **Results:** A total of 20 patients (17 females and 3 males) were enrolled in our study. There was a significant difference among tremor rate before and after intervention ($P = 0.001$). The drug was well tolerated and without any serious side effect during follow-up. **Conclusion:** Our findings suggest that although Levetiracetam caused a decrease tremor rate in MS it surged again after washout period.

Key word: Levetiracetam, multiple, sclerosis, tremor

INTRODUCTION

Multiple Sclerosis (MS) is the most common degenerative and inflammatory disease of the central nervous system which mainly affects individuals in youth ages.[1] One of the frequent symptoms of the disease is tremor which can severely cause disability and affect daily living and quality of life in individuals who have MS. The presence of tremor suggests a more aggressive course of the disease. Treatment of tremor in MS patients is still very challenging to manage.[2] The results of treatment with currently available medication in previous studies are often frustrating. Levetiracetam is a new antiepileptic and anticonvulsant drug.[3] The possible effect of Levetiracetam on MS patients is surveyed in a few previous studies.[4-6] However, the efficacy of Levetiracetam in treatment of MS-related tremor still remains controversial. In this study, we sought to determine if Levetiracetam is effective on treatment of tremor in patients with MS.

MATERIALS AND METHODS

Setting and patients

This clinical trial study was conducted from July 2012 to April 2012. We recruited 22 patients from Alzahra-Hospital, Isfahan, Iran.

Eligibility criteria included: A diagnosis of multiple sclerosis (according to the 2010 revised McDonald criteria);[7] an age of 18 to 55 years; a score of between 1 and 6 on the Kurtzke Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating more severe disability);[8] and existence of Holmes tremor in physical exam. Exclusion criteria were as follows: Prior use of Levetiracetam; past history of epilepsy; pregnancy or lactation; history of renal failure; any condition that would preclude safe and complete participation in the study; and lack of appropriate adherence to the study protocol. Definite MS for all of the participants was confirmed by two experienced neurologists. Furthermore, all of the patients were assessed for their EDSS and Tremor Rating Group Scale (TRGS) score before starting the intervention. Physical exam was done to prove existence of rubral tremor in participants.[5,6]

Intervention

Intervention was begun within 7 days of the screening visit. Eligible patients were given 500 mg Levetiracetam (Bakhtar Shimi Daroo Company Manufacture in Iran) twice a day for 1 week. The drug dosage increased 1000 mg per week until reaching the peak dose of 50 mg/kg. Then there was a 2 week period of washout (administration of Levetiracetam was discontinued for 2 weeks). After the washout period, first phase was repeated until reaching to peak point again (500 mg Levetiracetam twice a day for 1 week and increased 1000 mg per week until reaching the peak dose of 50 mg/kg).

Assessment

To evaluate tremor rate, we used TRGS (Tremor Rating Group Scale) scale with the total score computed

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from 0 (no tremor) to 68 (severe tremor, unable to stand without assistance). To determine the disability, we used the EDSS (which ranges from 0 to 10, with higher scores indicating more severe disability).We measured the TRGS four times: First, at the start point; second, 3 weeks after reaching to maximum dosage; third, after washout period and, forth, at the end of the study. We assessed participants at the same time of day to regulate food and medication.

Statistical analysis

The statistical analyses were performed using the SPSS software (version 20.0 shicago) Descriptive analyses were adopted for demographic and clinical characteristics reporting the variables as means ± 1SD. Kolmogrove-Smear Nov test were used for normality distribution variables (age, disease duration, EDSS). Differences among groups were assessed using repeated measures of ANOVA with the Tukey *post hoc* test. Pearson correlation was used for the relation between patients EDSS and tremor rate. A *P* value of less than 0.05 was considered the significance threshold.

Ethics

The study has been approved by the local ethic committee before initiation of the study. All participants are required to give informed written consent. No patient will be deprived of receiving a standard therapy.

RESULTS

Among 25 patients who were initially enrolled, two were excluded from the final analysis (lack of appropriate adherence to the study protocol). Three patients were not initially included; two with EDSS of more than six and the other one who was pregnant. A total of 20 patients (17 females and 3 males) completed the study. At inclusion, the mean ± SD age was 31.1 ± 8.2 years. The mean ± SD duration of the disease from the diagnosis to the study onset was 6.8 ± 4.9 years. The mean ± SD duration of having tremor was 2.6 ± 1.5 years and, the mean ± SD score of EDSS was 2.5 ± 1.6. The average of tremor in different times according to TRGRS scale is shown in Table 1.

Table 1: Average of tremor rate

Time	Tremor rate (mean±SD)
Onset of the study	28.3±11.6
3 weeks after first intervention	26.4±11.2
2 weeks washout	28.2±12.03
3 weeks after second intervention	27.1±11.5

There was a significant difference among tremor rate in different times of the study (*P*=0.001). It has decreased significantly after the first (*P*<0.001) and second three weeks of the intervention (*P*≤0.05). There was no significant difference in tremor rate after the washout period and onset of the study (*P*=0.64). Furthermore, Pearson correlation indicated that there is a direct relation between patients EDSS and tremor rate (*P*=0.001, r=0.639)

Safety

The drug was well tolerated and no serious adverse events were observed during follow-up.

DISCUSSION

Our findings suggest a significant difference in tremor rate before and after the intervention. It can be implied that the tremor rate have a declining tendency although it surged again after washout period. Tremor is one of the most challenging issues in MS patients; the treatment of which remains as a matter of debate.[2] There are a number of previous studies that evaluate efficacy of a range of drugs in treatment of MS related tremor, including primidone,[9] gluthetimide,[10] intrathecal baclofen,[11] and isoniazid.[12] The role of Levetiracetam on post-ischemic Holmes' tremor has been previously investigated;[4-6] though, there is no convincing evidence on such effects of this drug. Levetiracetam is an antileptic drug which also attrected the attention in MS because of its possible anti-inflammatory effect.[13] In experimental studies, different properties of Levetiracetam have been shown.[14] Likewise, there is a crossover study on six patients by Solaro *et al*., which showed the effect of Levetiracetam on the modification of kinetic parameters in MS patients. However; it was without functional improvement.[15] There is also a randomized, placebo-controlled, double-blind, crossover study which accomplished by Feys *et al*. in 14 patients with MS who received increasing dose of Levetiracetam. They evaluated the safety and efficacy of Levetiracetam and showed it is safe but ineffective for decreasing tremor severity in MS patients.[16] This is opposite of our findings. It may be because of the difference in inclusion criteria and long term of intervention and washout period.

CONCLUSION

In conclusion, this study indicated the possible effect of Levetiracetam on treatment of MS related tremor. Our results suggest that Levetiracetam can be considered as an additional option for treatment MS- related tremor. Notably it is well tolerated by MS patients and has a few side effects. The elucidation of the results is limited by small sample size, gender and, short duration of drug intake. Further studies with larger sample size in both genders in long-term duration needed to confirm this preliminary results and the mechanism of Levetiracetam in treatment MS-related tremor.

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