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Effects of lamotrigine on the symptoms and life qualities of the patients with post polio syndrome: A randomized, controlled study

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Abstract. The aim of this study is to find out if lamotrigine gives symptomatic relief and enhances quality of life in the patients with post-polio syndrome. Thirty patients were randomly assigned to receive or not to receive lamotrigine treatment. Lamotrigine at a daily dose of 50-100mg were given to the fifteen patients, and fifteen patients were used as the control group. Interventional advises and home exercises were given to all of the patients. Clinical assessments were made at baseline and repeated at the second and fourth weeks by the physician who was unaware of medication. The severity of pain, fatigue and muscle cramps were rated on a visual analogue scale. Health-related quality of life was measured using the Nottingham Health Profile. The patient's perceived level of fatigue was assessed using Fatigue Severity Scale. Comparing to the baseline values, statistically significant improvements were obtained in the mean scores of VAS, NHP and FSS at two weeks and four weeks in the patients on lamotrigine. No significant improvements were reported in the control group. These preliminary results indicate that lamotrigine relieves the symptoms and improves the life qualities of the patients with post polio syndrome.

Keywords: Post polio syndrome, lamotrigine, life quality, fatique

1. Introduction

Poliomyelitis is an acute illness caused by the neurotropic poliovirus, which infects the motor neuron pool at various levels of the neuraxis, with predilection to affect anterior horn cells of the spinal cord and motoneuron cell bodies in bulbar nuclei [7]. In recent years however, attention has been focused on the new musculoskeletal and neuromuscular symptoms reported 20–40 years after the paralytic poliomyelitis infection; what is now known as post-polio syndrome [17]. Many polio survivors now seek assistance for this new sympatology including fatigue, pain, and weakness of either previously affected muscles or previously clinically unaffected muscles. However, there is yet no medication that will relieve the symptoms, although some rehabilitation procedures may prove beneficial [1,2,36,37].

In spite of many clinical and electrophysiological studies, pathophysiological mechanisms underlying the delayed symptoms are poorly understood. Accelerated loss of the surviving motoneurons due to previous illness and subsequent compensatory adaptations have been the main focus in most of these studies [12,25, 33]. More recently, focal and/or specific loss of inhibitory interneurons between injured and normal motor neurons has been proposed to be a contributing factor [14]. Immunopathological mechanisms and the reactivation or persistence of poliovirus [12] have also been proposed theories to explain this new pathological phenomenon.

It is widely accepted that exitotoxicity, which refers to the ability of glutamate or related excitatory amino

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acids to mediate the death of central neurons after excessive exposure, plays an important role in the pathogenesis of several neurological diseases associated with neuronal death [11,20].

Results of the experimental studies demonstrated that neurodegeneration could be prevented by glutamate release blockers which inhibite endogenous glutamate release [31,32]. These findings have been supported by the clinical studies in which glutamate release blockers have shown promise in the treatment of either acutely developing cellular damages or slowly progressing neurodegenerative diseases [20–22]. However, the role of excitotoxicity in development of PPS or neuroprotective effect of glutamate release blockers have not been studied previously.

Lamotrigine is an approved, broad-spectrum antiepileptic drug that acts mainly through the inhibition of presynaptic neuronal sodium channels and thus inhibits glutamate release [15]. Experimental studies illustrated the possible neuroprotective effects of lamotrigine (LTG), by decreasing glutamate agonist-induced excitotoxicity [28,31]. Furthermore, several studies demonstrated that LTG has favorable effects on psychological well-being, produces positive effects on quality of life scales, and it is effective in relieving pain in a variety of chronic painful disorders [3–5,13,24,35]. These proven effects of LTG encouraged us to study this drug in a group of patients with PPS. We conducted this preliminary study in order to find out whether lamotrigine gives a symptomatic relief of the symptoms of PPS, thus enhances their quality of lives.

2. Methods

2.1. Study subjects

The study subjects were selected from among the patients admitted to Ege University Medical School, Department of Physical Medicine and Rehabilitation with the diagnosis of previous poliomyelitis. The patients were recruited to participate the study if they fulfilled the criteria for PPS; described by Halstead and Rossi [17] with 1: prior episode of paralytic polio 2: a period of neurological recovery followed by an extended interval of functional stability (at least 20 years) 3: the gradual or abrupt onset of neurogenic (non disuse) weakness in previously affected and/or unaffected muscles, accompanied or not by other new health problems such as excessive fatigue, muscle pain, joint pain, decreased endurance, decreased function and atrophy and 4: exclusion of medical, orthopedic, and neurological conditions that might cause the new health problems. Only the patients with lower extremity involvement were included. Non-ambulatory or wheelchair dependent patients and the patients with significant medical illnesses such as coronary artery disease, liver and kidney disease, malignancy, or medical or surgical conditions which could be contributing to any secondary deterioration in muscle performance were excluded. Thirty post-polio subjects who met these selection criteria were included in the study.

All patients answered a detailed questionnaire concerning their social situation, original illness and subsequent sequel, previous operations related to polio, use of orhotics and/or walking aids and new neuromuscular and musculoskeletal complaints. Physical examination including visual inspection for muscle atrophy, manual muscle testing of selected upper and lower limb muscle groups, deep tendon reflexes and sensation were performed in all patients. Needle EMG studies of the selected muscles were performed by an experienced electromyographer.

2.2. Study design

The subjects were randomly assigned to receive or not to receive lamotrigine treatment. Fifteen patients constituted the active medication group after obtaining informed consent. Remaining fifteen patients were used as the control group. Interventional advises including pacing, energy conservation, use of orthotic devices and weight loss were given to all of the patients depending on their specific clinical situations. A home exercise program consisting of submaximal isometric and/or progressive resistive exercises which was defined according to any individual patient's characteristics was recommended to each patient. Clinical assessments were made at baseline; and repeated at two weeks, and four weeks by the physician who made the initial assessments and who was unaware of medication.

2.3. Clinical assessments

Patients were asked to rate their severity of pain, fatigue and muscle cramps during the past week, on a visual analogue scale (VAS) of 10 mm.

Health-related quality of life was measured by using the Nottingham Health Profile (NHP), which is a self-administered questionnaire. A Turkish version of NHP has been found to be valid and reliable [23]. The

Table 1
Demographic data of the two groups at study enter (mean ± SD)

	LTG group	Control group
Age (years)	36.6 ± 11.3	35.9 ± 12.4
Duration until the onset of new symptoms (years)	39.9 ± 19.2	38.9 ± 15.2
Duration since onset of new symptoms (months)	12.1 ± 15.2	16.4 ± 17.6

NHP is divided into two parts. Only the first part of the NHP was used in this study. It contains 38 questions that convey limitations of activity or aspects of distress in six dimensions (emotional reaction, sleep, energy, pain, physical mobility and social isolation). For each question, the answer is computed as yes or no; indicating the presence or absence of the problems the patients are experiencing at the time they are completing the questionnaire. A score in the range of 0–100 for each dimension as well as a total score for all dimensions can be calculated; with higher scores indicating greater level of distress.

The patient's perceived level of fatigue was assessed using Fatigue Severity Scale (FSS) FSS assesses the level of fatigue and monitors its change over time or in response to therapeutic interventions. It consists of nine items assessing the general effect of fatigue on daily activities such as motivational decrease, prevention of physical functioning and interference with socioeconomic factors during the past week. The answers to the different items are recorded between 1 (strongly disagree) and 7 (strongly agree). FSS score is calculated from the mean value; giving the maximum score of 7. The higher is the score, the greater is the fatigue severity.

2.4. Lamotrigine treatment

Lamotrigine (LTG) treatment was started at a daily dose of 50 mg. The dose was increased to 100 mg/day after two weeks. Blood samples were taken for liver and kidney function tests and complete blood count after the first week, and repeated at the fourth week in order to evaluate the possible side effects of the medication.

2.5. Statistical analysis

Data were statistically analyzed by using SPSS/PC V10.0. For all categorical variables, among group differences at baseline were analyzed using Mann Whitney-U test. Within-group change for repeated measures was analyzed by using the Friedman test. A level of 0.05 was accepted as significant. If it was determined that differences exist among the repeated measures within-group by Friedman test, then Bonferroni adjusted Wilcoxon signed-rank test was performed to determine the differences from baseline values; a level of 0.025 was accepted as significant.

Table 2
The sypmtoms reported by the post polio patients included in the study ($n = 30$)

Symptom	n	%
Fatigue	30	100
New weakness	26	86.6
Non-involved limb only	5	19.2
Involved limb only	4	15.3
Both involved and non-involved limbs	17	65.3
Cramps	25	83.3
Pain at the lower extremities	24	80.0
Cold intolerance	9	30.0
Sleep disturbances	7	23.3

3. Results

3.1. Baseline assessments

Table 1 shows the demographic data of the post polio patients included in the study. There were no statistically significant differences between the two groups regarding the mean age, the average duration until the onset of new post polio symptoms and the average time since onset of new symptoms ($p > 0.05$).

Detailed questioning by the physician revealed that the most commonly acknowledged new symptoms were fatigue, weakness, muscle cramps and pain (Table 2). Of the 30 patients with PPS, 23 were experiencing late-onset weakness in the muscles that were clinically affected by polio previously while 25 noted weakness in the muscles that they had previously considered normal. Needle EMG investigations typically demonstrated the evidence of extensive prior denervation and reinnervation in previously affected and supposedly unaffected limbs.

Table 3 demonstrates the baseline values of the clinical scores in both groups. The results of the VAS demonstrated the presence of moderate to severe pain, fatigue, weakness and muscle cramps in the postpolio patients. Although the VAS scores were generally higher in the lamotrigine group comparing to the con-

Table 3
Mean and standard deviation values of the clinical scores at baseline and at follow-up visits in both groups

Scale	Lamotrigine group			Control group		
	baseline	two weeks	four weeks	baseline	two weeks	four weeks
VAS						
fatigue	7.1 ± 3.6^{a}	$3.6 \pm 2.8^{*}$	$3.0 \pm 2.9^{*}$	4.2 ± 3.8	3.9 ± 3.7	4.0 ± 3.5
pain	5.6 ± 3.2	$2.1 \pm 1.8^{*}$	$1.6 \pm 1.5^{*}$	4.5 ± 2.9	4.0 ± 2.8	4.4 ± 2.7
cramp	4.2 ± 3.5	$1.1 \pm 1.3^{*}$	$0.9 \pm 1.1^{*}$	4.4 ± 3.7	4.1 ± 3.5	4.2 ± 3.5
NHP						
mobility	37.8 ± 15.3	$21.7 \pm 16.1^{*}$	$14.7 \pm 13.3^{*}$	38.1 ± 18.1	38.1 ± 18.9	38.4 ± 18.8
pain	50.3 ± 36.7	$15.5 \pm 23.8^{*}$	$7.9 \pm 14.1^{*}$	35.2 ± 35.7	38.1 ± 18.9	38.4 ± 19.6
sleep	22.9 ± 36.1	$9.6 \pm 25.7^{*}$	$2.9 \pm 6.2^{*}$	28.0 ± 30.9	28.4 ± 32.2	27.8 ± 32.1
energy	68.7 ± 37.5^{a}	$6.6 \pm 14.1^{*}$	$2.4 \pm 6.7^{*}$	37.9 ± 39.8	34.7 ± 38.6	35.7 ± 38.6
social	11.3 ± 18.8	$2.9 \pm 7.7^{*}$	$00 \pm 00^{*}$	11.1 ± 18.7	8.1 ± 15.1	7.1 ± 12.9
emotional	27.5 ± 34.1	$5.1 \pm 12.1^{*}$	$2.6 \pm 4.5^{*}$	23.6 ± 26.7	19.5 ± 26.0	18.6 ± 24.7
total score	218.6 ± 118.4^{a}	$74.0 \pm 78.3^{*}$	$35.0 \pm 36.1^{*}$	174.3 ± 125.5	166.2 ± 113.2	166.4 ± 109.1
FSS						
total score	5.2 ± 0.9^{a}	$3.1 \pm 1.4^{*}$	$2.5 \pm 1.1^{*}$	3.9 ± 1.7	4.3 ± 1.2	3.9 ± 1.3

NHP: Nottingham Health Profile.
FSS: Fatigue Severity Scale.
VAS: Visual Analogue Scale.
[a]Statistically significant differences between the two groups ($p < 0.05$).
[*]Statistically significant change from baseline ($p < 0.025$).

trol group; only the difference in fatigue severity was found to be statistically significant ($p < 0.05$). Supporting this finding, fatigue severity was found to be greater in the medication group comparing to the control group as demonstrated with the significantly higher total score of FSS ($p < 0.05$). NHP demonstrated the highest distresses in the dimensions of physical mobility, energy and pain. The least distress was in the social isolation dimension; only six patients have reported some difficulties in social interactions. Although the lamotrigine group tended to have higher scores compared to the control group, the difference reached the significant level for the total score and the energy subdimension ($p < 0.05$).

3.2. Follow-up assessments

Table 3 demonstrates the mean values and standard deviations of the clinical scores at scheduled follow-up visits in both groups. All subjects on lamotrigine reported significant symptomatic relief with decreased level of fatigue, pain and muscle cramps on VAS at two weeks ($p < 0.025$). Symptom relief was more pronounced at four weeks ($p < 0.025$). No statistically significant changes were reported in the VAS scores in the control group ($p > 0.05$).

In the lamotrigine group, highly significant improvements were noted in the total score and in all of the sub dimensions of NHP at follow-up comparing to the baseline values ($p < 0.025$). On the other hand, no statistically significant improvements were noted in the control group throughout the study ($p > 0.05$). In terms of the total scores of FSS, statistically significant improvements were noted at two weeks and four weeks in the lamotrigine group ($p < 0.025$), while no statistically significant improvements were found in the control group ($p > 0.05$).

Lamotrigine at a dose of 100 mg daily was well tolerated and no undesired major or minor side effects were reported.

4. Discussion

The results of the present study shows that lamotrigine at a daily dose of 50 to 100 mg relieves the symptoms of PPS and significantly improves the quality of life. Consistent throughout previous literature, the mostly reported new symptoms were fatigue, weakness, pain and muscle cramps in our patients with PPS and the new symptoms and electrophysiological abnormalities were not constricted to areas previously considered weakened by polio [1,26]. Recent studies have shown that the new symptoms of PPS increase the patient's disability to perform daily activities and decreased their satisfaction with life [8,16,34]. In most of these studies, distress in aspects of perceived health has been measured by using the NHP [8,16]; most distresses have been found in the dimensions of physical mobility, pain, energy and emotional reactions. The im-

pact has mainly been on mobility-related activities [16]. In the present study, NHP questionnaire was chosen in an attempt to capture the whole range of outcomes from symptomatic limitations of physical abilities to overall well-being and health related quality of life. Although we did not compare the results with those obtained from normal population or with the polio patients without the symptoms of PPS, the highest distresses were found in the dimensions of physical mobility, energy and pain. Difficulty in stair climbing was almost universal. In the dimension of pain, items involving physical mobility were those that contributed most to the level of distress. The results from the NHP questionnaire also reflected that many individuals participated in social activities. These findings were consistent with the results of the previous studies [8,16].

FSS has been used to assess the level of fatigue in patients in any disorder related to fatigue including poliomyelitis [10,19,29,30]. Therefore we judged that it might be useful to measure fatigue related to PPS and to assess the change in the severity of fatigue in response to lamotrigine treatment. High scores were reported on FSS indicating a great fatigue severity in our patients; the scores seemed to be higher comparing to the Parkinson disease [19] and were comparable to the other results reported in patients with poliomyelitis sequelae [29,30].

In this study, all patients on lamotrigine reported decreases in their fatigue, pain and muscle cramps on VAS at two weeks after initialization of the treatment, which was sustained throughout the study. In accordance with the improvements reported on VAS, significant reductions in the pain and energy scores were reported on the NHP. The decrease in the severity of fatigue has been supported by the significant decreases in the FSS scores. There were also significant improvements in physical mobility and emotional reactions in response to lamotrigine treatment, and the patients reported that they were sleeping better. Related to these improvements, all of the patients reported that they had started participating social activities more. At two weeks, only one patient reported minor difficulty in participating social activities that was resolved at four weeks.

Although most of the antiepileptic drugs have negative effects on behaviour spesifically on cognition, several studies have demonstrated favorable effects of lamotrigine on physical well being and cognitive functioning [3–5,24]. LTG has been reported to produce general psychostimulant effect demonstrated with improved cognitive activation and "activating" mood changes in healthy volunteers [5,24]. Furthermore, it has been reported to produce positive effects on quality of life scales in healthy volunteers [18,27]. Cognitive activation effects of LTG have been assumed to be related to the predominance of glutamate excitatory neurotransmission as the dominant mechanism of action. These positive effects of lamotrigine on cognitive functioning and mood led the use of the drug in psychiatry for the treatment of depression, apathy hypersomnia and fatique [9]. In our study, the effect of LTG on the cognitive functions of PPS patients have not been assessed by special cognitive tests; but the energy, sleep and emotional reaction scores of the NHP improved in all patients after use of LTG.

LTG has been found to be effective in relieving the pain associated with acut and chronic painful conditions, especially the pain with neuropathic origin [6,13, 35]. Its antinociceptive properties have been assumed to be related to its stabilizing effect of the neural membrane through blocking activation of voltage-sensitive sodium channels and its inhibiting effect of the presynaptic release of glutamate [28]. 80% of our patients with PPS have had pain and cramping at the lower extremities, getting worse during or after physical excertion. The relationship between physical activity in daily life and experience of pain in PPS patients has been documented [16]. Thus advises were given to the patients to modify their level of physical activity. This may be the reason for the decreased level of pain after lamotrigine treatment. However, no significant improvement in pain severity was noted in the patients to whom the same interventional advises were given. It thus appears that lamotrigine is effective in relieving pain related to PPS.

The selected initial dose of LTG in this study was 50 mg daily, a dose that has been used in the studies on healthy adult population [28,33,34]. The dose was increased after two weeks and maximum dose of 100 mg daily was reached. Even with the higher doses, the safety profile of LTG has been shown to be generally acceptable [38]. In the present study no adverse reactions were observed with a dose of 50–100 mg and the treatment was well tolerated. Although the dose used in this study was lower than the clinical dose that is used in patients with epilepsy, beneficial effects on the symptoms of PPS were obtained. It should be clarified if the higher doses are associated with higher beneficial effect and increased risk of side effects.

This study is the first report investigating the use of LTG in patients with PPS, supporting that LTG together with exercise and other interventional advises are effective in relieving the symptoms of PPS and thus en-

hance the health related quality of life. It should be noted that, although our results are encouraging, they should be viewed cautiously because the study does have limitations. 1. Muscle strength was evaluated by manual muscle testing. Although the patients reported decreased level of weakness, the minor differences in muscle strength could not be detected by manual muscle testing. Evaluation of the strength by dynamometer or by isokinetic devices might have given the opportunity to assess the differences in muscle strength. 2. The study could not demonstrate whether neuroprotective effect of lamotrigine might offer a protection against further neuronal loss in PPS. This study may give encourage for further studies investigating the role of exitotoxicity in the pathogenesis of further motor neuron loss and deterioration in muscle performance in PPS. Further studies should also evaluate the change in motor unit numbers in response to lamotrigine treatment. 3. This preliminary study was performed in a small number of subjects with PPS and follow-up period was quite short. 4. Because placebo control was not used, it cannot be excluded that improvements were due to a placebo effect. Nevertheless, the same interventional advises and home exercise program were given to the patients who did not received the lamotrigine treatment. Since no significant improvements were noted in these patients, the improvements could be attributed to the beneficial effects of lamotrigine treatment. This study would prompt randomized, placebo controlled studies assessing this potential therapeutic effect and the long-term efficacy of LTG in larger series is yet to be assessed.

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