IJMS
Vol 35, No 4, December 2010

Original Article

The Effects of Lamotrigine on Pain, Sleep, and Mood in Refractory Form of Central Post-Stroke Pain Syndrome

Peyman Petramfar, Ali Reza Nikseresht, Ehsan Yaghoubi

Abstract

Background: Central post-stroke pain (CPSP) is a distressing pain syndrome, sometimes become refractory to the conventional pain managements. Anticonvulsants have been used to alleviate different central pains. Lamotrigine is a novel anticonvulsant and its proper dosage and its efficacy have not been well studied yet. The aim of this study was to evaluate the effect of 100 mg lamotrigine on refractory form of CPSP.

Methods: The medical files of 17 patients with CPSP who had not responded to the other drugs and were treated with lamotrigine were studied. Using Brief Pain Inventory, pain, sleep and mood were assessed before, and after 8 and 24 weeks of treatment.

Results: After 24 weeks, 70.5 % of the patients responded to lamotrigine, and there was an improvement of 2.41 in the mean score of average pain (P=0.001).

Conclusion: Lamotrigine 100 mg daily was effective in the treatment of refractory CPSP, and might be prescribed before planning for more aggressive surgical managements.
Iran J Med Sci 2010; 35(4): 299-303.

Keywords ● Pain ● lamotrigine ● sleep disturbance ● mood disorder

Introduction

Thalamic syndrome was first described as a condition that follows a thalamic stroke with excruciating pain in the contralateral half of the body.[1] The term "thalamic pain" has been replaced by "central post-stroke pain" (CPSP).[2] Central post-stroke pain is unique because of its diversity, which is reflected in its clinical picture, latency from the onset of stroke, pathophysiological mechanisms and treatment options. It can result in disability and interference with rehabilitation, and adversely affect the quality of life. The pathophysiology of CPSP is not well understood but central disinhibition, imbalance of stimuli and central sensitization have been suggested.[3]

Central post-stroke pain is difficult to treat, and pain reduction rather than pain relief is the goal of the treatments. This emphasizes the need for different trials of therapy and better result. Conventional analgesics were mostly ineffective, and long-term opioid treatments have been noted to be effective in a minority of patients.[4] Gabapentin has been tried in a randomized, placebo-controlled trial of 305 patients with chronic pain, 9 patients

Department of Neurology,
Shiraz University of Medical Sciences,
Shiraz, Iran.

Correspondence:
Peyman Petramfar MD,
Department of Neurology,
Shiraz University of Medical Sciences,
Shiraz, Iran.
Tel/Fax: +98 711 6121065
Email: petramfar@sums.ac.ir
Received: 10 April 2010
Revised: 7 June 2010
Accepted: 12 August 2010

who had CPSP.[5] The study showed that gabapentin was well tolerated, but did not significantly result in the improvement of the pain.[5]

Numerous drugs have been tried to treat CPSP, but large controlled trials are still lacking, and the treatment is far from being standardized. The possible hyperexcitability of the damaged nervous system has been the rationale for studies on the use of anticonvulsants and local anesthetic agents for the treatment of CPSP.

Lamotrigine, first described as an anticonvulsant, is effective in managing chronic pains. Its mode of action is via inhibitory effect over the voltage gated sodium channel and an inhibition of glutamate release. It was successful in the treatment of trigeminal neuralgia, diabetic neuropathy and human immune deficiency virus induced neuropathy.[6-8] There are a number of case reports and small case series in the literature, which support the effect of lamotrigine on CPSP.[9,10]

The aim of the present study was to evaluate the effects of lamotrigine on the pain, sleep and mood disturbances in patients suffering from refractory form of CPSP.

Patients and Methods

Patients

The study is a retrospective analysis of medical records of 17 patients (10 females and 7 males) with CPSP referring to Motahari Clinic, Shiraz University of Medical Sciences from January 2006 to November 2008. The ages of the patients were 60.2±12.4 years, and the mean duration of CPSP was 8.4 months (range: 4-20 months).

The diagnosis of CPSP was based on the presence of pain in an area of the body with sensory loss explained by a specific central nervous system lesion and no nociceptive, peripheral neurogenic or psychogenic component of the pain.[11] Patients who had a history of previous stroke, which had been confirmed by the neuroimaging, and infarction involving brain stem, thalamus or parietal lobe were included. Those with a history of previous seizure and sensitivity to anticonvulsants, prior consumption of lamotrigine, clinically relevant hepatic or renal dysfunction, and clinical improvements by other medications were excluded. Moreover, those who lacked a reliable care-giver were excluded as well.

The pain had started within 2 months after a stroke. All patients had either taken simple analgesics, opioid-based analgesics, gabapentin, and tricyclic antidepressants such as amitriptyline, with no significant improvement in the severity of their pain, or could not tolerate the side effects of these drugs. All patients were informed about the objectives and risks of the study and the side effects of lamotrigine, and written consents were obtained from the patients or their first-degree relatives.

Methods

All patients received lamotrigine for 24 weeks. They received 25 mg daily for the first 2 weeks, 50 mg daily for the second 2 weeks, 75 mg daily for the fifth week, and 100 mg daily for the rest of the study (19 weeks). The patients' pain, sleep and mood disturbances were recorded 3 times; before the initiation of treatment with lamotrigine, after 8 weeks inside the treatment, and at the end of the study using Brief Pain Inventory (BPI) (with permission, Charles S. Cleeland, Pain Research Group).[12] The BPI is a widely used numeric rating scale, which measures the severity of pain as the worse, average and least ones as well as its interference with daily functions such as sleep and mood. Each BPI item uses a 0 to 10 for severity of the pain and its interference with sleep and mood. A zero score indicate no pain and no interference, and a score of 10 indicate a pain as bad as you can imagine and complete interference. The worst, average and least pain as well as mood and sleep disturbances due to pain for every patient were recorded.

Statistical Analysis

Data are presented as the mean±SD. The rate of improvement between two times of measurement was calculated by subtraction of mean values at the two occasions. One way Analysis of Variance (ANOVA) with repeated measurement was used to compare the effects of drugs at 3 time points. The pairwise comparisons were carried out using paired t test with Bonferroni correction. A P value of ≤ 0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS) was used to analyze the data.

Results

The severity of pain, namely the worst, average and the least at the beginning of the treatment were 8.2±0.66, 6.8±0.8, and 4.2±0.98, respectively. Eight weeks of treatment with lamotrigine resulted in significant (P=0.001) decrease of worst (-2.35±1.86), average (-2.23±1.85) and least (-1.35±1.45) pains. It was also associated with significant (P=0.001) improvement in the disturbances of mood (-2.47±1.73) and sleep (-2.76±1.88) (table 1).

Table 1: The values (mean ± SD) of scores for pain (worst, average, and least), mood and sleep of the patients with central post-stroke pain after 8 and 24 weeks of treatment with lamotrigine.

	Before Treatment	After 8 Weeks	After 24 Weeks
Worst Pain	8.23±0.66	5.88±1.57	5.58±1.83
Average Pain	6.82±0.8	4.58±1.54	4.41±1.62
Least Pain	4.29±0.98	2.94±1.14	3.29±0.91
Mood	8.64±0.86	6.17±1.55	4.52±1.41
Sleep	8.47±0.51	5.70±1.53	5.94±1.95

Compared to the severity of pain after 8 weeks of treatment, 24 weeks of treatment did not change the severity of pain significantly (P>0.05). However, the score for mood disturbance after 24 weeks was significantly (P>0.001) lower than that after 8 weeks of treatment (figure 1-3). The rate of improvement in pain, mood and sleep were more in the male than in female participants, but the difference did not reach statistical significance (P>0.05).

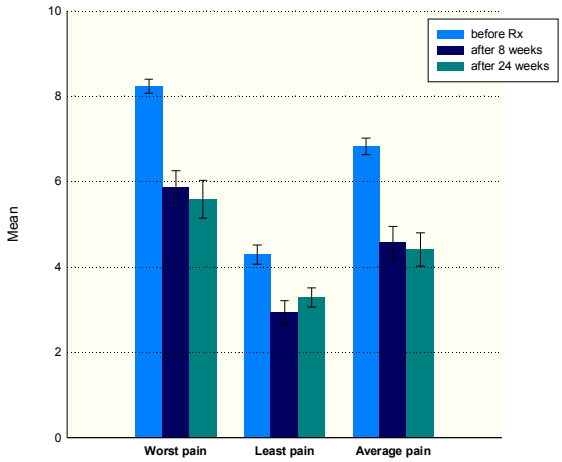

Figure 1: Severity (Mean and confidence interval) of pain before, and after 8 and 24 weeks of treatment with lamotrigine in patients with central post-stroke pain

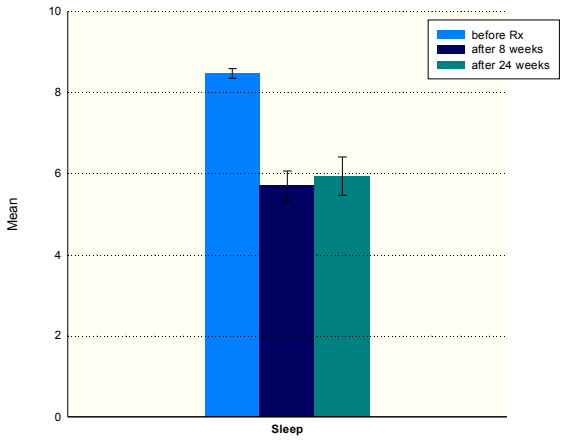

Figure 2: The levels (Mean and confidence interval) of sleep disturbance before, and after 8 and 24 weeks treatment with lamotrigine in patients central post-stroke pain

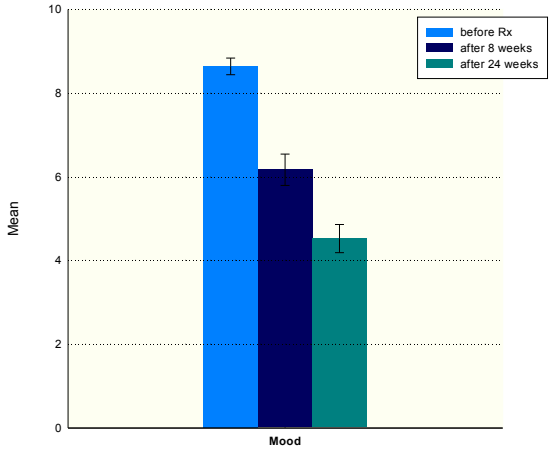

Figure 3: The levels (mean and confidence interval) of mood disorder before, and after 8 and 24 weeks treatment with lamotrigine in patients central post-stroke pain

One patient discontinued the drug due to somnolence and dizziness. None of the patients reported skin rash, but 23% of them complained of somnolence and fatigue and 12% of nausea. After 24 weeks, 4 patients (23.5%) reported no change in the severity of the pain and almost no change in their mood and their sleep quality. Seventy five percent (3 out of 4) of them had infarction in the thalamus.

Discussion

The findings of the present study suggest that lamotrigine at 100 mg daily could reduce the worst pain score as much as -2.64±1.99 after 24 weeks in patients whose pain was refractory to previous treatments. Moreover, the treatment was associated with significant improvements in mood and sleep disturbances. Due to proper dosage titration, lamotrigine was well tolerated by the patients in this study. Minor side effects, which did not require the cessation of drug's consumption, developed in a minority of the patients. Central pain syndromes were thought to be intractable for many years, till their response to medical treatment were shown.[13] However, many of these patients do not respond to current therapies, and alternative treatments seem to be

necessary. We evaluated sleep and mood disturbances, which may be the most important facts in daily living of old population. The importance of such disturbances is more pronounced for the patients with an age range used in the present study. Lamotrigine caused a significant improvement in the quality of sleep and mood. However, mood disorders may benefit from continuing the drug which can be due to antidepressant effect of lamotrigine.

The effect of lamotrigine on CPSP was also evaluated by Vertergaard and colleagues.[14] They found that lamotrigine 200 mg daily reduced the median pain score to 5, compared to a score of 7 in group receiving placebo. They used a higher dosage of lamotrigine as the first line drug in the treatment of CPSP, but the present study used a lower dosage in patients with refractory form of CPSP. A comparison of the finding of the two studies might suggest that there is no difference in the effects of 100 and 200 mg of lamotrigine in the treatment of CPSP.

Other criteria in BPI such as inability to work and to walk independently, decreased social contact, and decreased enjoyment of life are the result of functional disabilities in most stroke patients and not related to CPSP. Therefore, we decided not to evaluate these items as they are routinely assessed in BPI.

Surgical treatment of refractory CPSP such as motor cortex stimulation and deep brain stimulation (DBS) showed about 50 to 75% improvement in central pain,[15,16] more than what was achieved medically. However, considering the potential serious side effects of an invasive procedure of motor cortex stimulation, and the high cost of such procedures, it would be logical to manage patients with all available medical treatment first. In addition, in a meta analysis, which evaluated the role of DBS in chronic intractable pain, it was found that BDS was more effective in nociceptive pain compared to deafferentation pain such as CPSP.[17]

The present study did suffer from a number of shortcomings including the absence of a placebo-receiving group and small sample size. The lack of a placebo-receiving group was due to ethical limitation to devoid a group from receiving proper treatment. However, it would have been more rational if other drugs had been used as a control group for lamotrigine-receiving group. The small sample size was due to strict inclusion criteria and rareness of CPSP.

Conclusion

The findings of the present study indicate that lamotrigine given 100 mg daily might be effective in the treatment of patients suffering from CPSP, who could not tolerate the side effects of their previous treatments, or their symptoms did not improve with other drugs. The findings also showed that lamotrigine did improve the quality of sleep and mood, thereby the quality of life. The finding might also be taken as evidence to suggest that lamotrigine be prescribed before scheduling the patients for any surgical or more aggressive management.

Acknowledgement

The authors would like to thank Dr. Vosughi, Mrs. Ghorbani, and Miss Gholami of the Center for Development of Clinical Research at Nemazee Hospital, Shiraz, Iran.

Conflict of Interest: None declared

References

1 Wilkins RH, Brody IA. The thalamic syndrome. *Arch Neurol* 1969; 20: 559-62.
2 Kit H, Finnerup NB, Jensen TS. Central-post stroke pain: clinical charactrestics, pathophysiology, and management. *Lancet Neurol* 2009; 8: 857-68.
3 Frese A, Husstedt IW, Ringelstein EB, Evers S. Pharmacologic Treatment of Central Post-Stroke Pain. *Clin J Pain* 2006; 22: 252-60.
4 Attal N, Guirimand F, Brasseur L, et al. Effects of IV morphine in central pain: a randomized placebo-controlled study. *Neurology* 2002; 58: 554-63.
5 Serpell MG. Neuropathic pain study group. Gabapentin in neuropathic pain syndromes; a randomized, double-blind, placebo-controlled trial. *Pain* 2002; 99: 557–66.
6 Jose VM, Bhansali A, Hota D, Pandhi P. Randomized double-blind study comparing the efficacy and safety of lamotrigine and Amitriptyline in painful diabetic neuropathy. *Diabet Med* 2007; 24: 377-83.
7 Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled cross-over trial. *Pain* 1997; 73: 223-30.
8 Simpson DM, Olney R, McArthur JC, et al. A placebo-controlled trial of lamotrigine for painful HIV-associated neuropathy. *Neurology* 2000; 54: 2115-9.
9 Canavero S, Bonicalzi V. Lamotrigine control of central pain. *Pain* 1996; 68: 179-81.
10 Carrieri PB, Provitera V, Lavorgna L, Bruno R. Response of thalamic pain

syndrome to lamotrigine. *Eur J Neurol* 1998; 5: 625-6.
11 Leijon G, Boivie J, Johansson I. Central post-stroke pain. Neurological symptoms and pain characteristics. *Pain* 1989; 36: 13-25.
12 Cleeland CS. Pain assessment in cancer. In: Osoba D, ed. Effect of cancer on quality of life. Boca Raton, FL: CRC Press, 1991: 293-305.
13 Leijon G, Boivie J. Central post-stroke pain: a controlled trial of Amitriptyline and carbamazepine. *Pain* 1989; 36: 27-36.
14 Vestergaard K, Andersen G, Gottrup H, et al. Lamotrigine for central post-stroke pain: A randomized controlled trial. *Neurology* 2001; 56: 184-90.
15 Saitoh Y, Shibata M, Hirano S, et al. Motor cortex stimulation for central and peripheral deafferentation pain: report of eight cases. *J Neurosurg* 2000; 92: 150-5.
16 Nandi D, Aziz T, Carter H, Stein J. Thalamic field potentials in chronic central pain treated by periventricular gray stimulation – a series of eight cases. *Pain* 2003; 101: 97-107.
17 Bittar RG, Kar-Purkayastha I, Owen SL, et al. Deep brain stimulation for pain relief: a meta-analysis. *J Clin Neurosci* 2005; 12: 515-19.