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Original Article

The Efficacy of Gabapentin in Patients with Central Post-stroke Pain

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Abstract

Thalamic pain syndrome, a type of central post-stroke pain (CPSP), may develops after a hemorrhagic or ischemic stroke and results in impairment of the thalamus. There is limited experience about gabapentin in treatment of central pains like CPSP.

In a prospective observational study, the intensity of pain was recorded using the Numeric Rating Scale (NRS) at the entrance to the study. Patients eligible for treating with gabapentin, received gabapentin 300 mg twice-daily. The pain intensity was measured at entrance to the study and after one month using NRS. Decrease of 3 points from the initial NRS considered being clinically significant.

From a total of 180 primarily screened patients, 84 (44 men and 40 women) were recruited. There was a significant difference between pre-treatment and post-treatment NRS (5.9 ± 2.51 vs. 4.7 ± 3.01; 95% CI: 0.442-1.962, p = 0.002). Fisher›s exact test showed no statistically significant effect of clinical and demographic characteristics of patients on their therapeutic response to gabapentin.

Given the safety, efficacy, well tolerability and lack of interaction with other drugs we suggest gabapentin to be more considered as a first line therapy or as add-on therapy for reducing the pain severity in patients with thalamic syndrome.

Keywords: Gabapentin; Central nervous system; Cerebrovascular accident; Central post stroke pain.

Introduction

Central post-stroke pain (CPSP) can be defined as a central neuropathic pain condition occurring after stroke characterized by pain and sensory abnormalities where other causes of obvious nociceptive, psychogenic, or peripheral pain have been excluded (1, 2). The prevalence and yearly incidence of CPSP have been reported as 7.3% and 8%, respectively (2, 3) and occurs in 8%–14% of patients with stroke (4). CPSP is considered challenging from a clinical management standpoint and existing treatment options do not result in optimal outcomes (5, 6).

Although it is more than a century after the first description of the thalamic syndrome, the evidence for treatment of this pain syndrome is

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still extremely diminutive. Pain medications often provide some reduction of pain, but not complete relief of pain, for those affected by central pain syndrome. Opioids, tricyclic antidepressants such as amitriptyline or anticonvulsants such as lamotrigine and gabapentin have been used in patients with CPSP (7, 8). Because of potential side effects, long-term use of IV drugs such as lidocaine, propofol and ketamine have been limited; although they might be beneficial for short therapeutic episodes (7). Few pilot studies have reported Kampo medicine (9) and vestibular caloric stimulation (10) as effective treatments in patients refractory to conventional pharmacologic treatments. Despite several studies and reports debate continues about the best strategies for the management of CPSP and there are still too few large-scale comparative studies (6).

Gabapentin and pregabalin, safe and partially well tolerated antiepileptic agents, have shown efficacy in several neuropathic pain conditions (11-14). It has been approved as adjunctive therapy in the treatment of partial seizures and for the management of postherpetic neuralgia (15) and currently is also used for modulating the peripheral and central neuropathic pains (16) and relieving withdrawal-related pain due to heroin use (13).

Despite several studies of gabapentin in the area of neuropathic pain, far too little attention has been paid to its role in CPSP. Serpel *et al.* in a randomized, placebo-controlled trial of 305 patients with chronic pain, 9 of whom had CPSP, evaluated the efficacy and safety of gabapentin in the treatment of neuropathic pain. But the effect of gabapentin was not significant in patients suffering CPSP (17). Usefulness of gabapentin, however, has been reported in a 45-yr old man with CPSP who was refractory to phenytoin, carbamazepine, and sodium valproate (8).

The aim of this study was to determine the efficacy of gabapentin in the management of patients suffering CPSP with regard to reduction in numerical rating scale for pain scores (NRS).

Experimental

Study design and setting

This was a prospective observational study conducted in multi centers at Tehran, Iran. Participating centers were two outpatient clinics from two different educational hospitals and three private neurology clinics in Tehran, Iran. Approval of this study was conducted by the institutional review board of all of the participating centers. All patients were given a written informed consent before entering the study, and the study was performed in accordance with the declaration of Helsinki.

All patients with stroke in the thalamic area admitted to each center between January 7, 2010 and June 30, 2011 were evaluated. Patients documented as being diagnosed with CPSP and who found to be eligible for treating with gabapentin as their standard therapy, entered to the study and demographic information (age, gender), stroke type, NRS on day of diagnosis, and NRS 30-day after treatment initiation were documented.

Management of the patients was based on EFNS (European Federation of Neurological Societies) guidelines on the pharmacological treatment of neuropathic pain (6). According to each patient's condition and comorbidities and past medical history, appropriate analgesic drug, which was one anticonvulsant or tricyclic antidepressant, was given as their standard therapy.

If a patient with an initial treatment other than gabapentin had no clinical response to the drug, a proper response was defined as at least three points decline in NRS, the therapeutic course was discontinued. NRS was recorded again and gabapentin was started for the patient. Finally, one month after initiation of gabapentin, the NRS of the patients were documented.

Study population

Patients were qualified for the study on the basis of these inclusion criteria: (I) positive history of hemorrhagic or ischemic stroke in the thalamic area proved by computed tomography or magnetic resonance imaging of the brain; (II) presence of signs and symptoms in accordance with a decrease in pain and heat sensations in the affected part of the body; (III) presence of spontaneous or stimulated pain in the affected side (contralateral to the thalamic involvement) which could be smaller or the same in size as the

sensory impairment area; and (IV) a pain onset after a thalamic stroke.

Exclusion criteria comprise lack of imaging findings compatible with stroke and other imaging abnormalities including tumors in the thalamus area; absence of sensory impairment in the affected side of the body; therapeutic response to other treatments of thalamic syndrome; and previous hypersensitivity to gabapentin. Women were excluded if they were pregnant or lactating during the study. Eligible patients received gabapentin 300 mg twice daily for one month.

Outcome measures

The primary outcome in this study was the change in the NRS from the baseline through the fourth week of treatment and the secondary outcome was the proportion of patients with a clinically significant change in NRS (three-point decrease).

Statistical analysis

Comparison was done using the paired sample t-test. Two-sided 95% confidence interval (CI) for the difference in response rates was calculated. A p-value of < 0.05 was needed for a result to be considered statistically significant. In the second step of our analysis, patients with a proper response and those who did not response to the suggested treatment were compared with regard to their baseline characteristics to find any probable correlation. To perform this comparison, unpaired t-test was used for interval variables and Chi-square or Fisher›s exact test was used for nominal data.

Results

Study patients

Of all 180 primarily screened patients, 93 patients entered to the study of whom 9 did not complete the study during the follow up period, and 84 patients successfully completed the study (Figure 1).

Among patients 44 (52.4%) men and 40 (47.6%) women completed the study. Type of underlying stroke that caused thalamic syndrome was ischemic in 76 (90.5%) patients and hemorrhagic in 8 (9.5%) patients. Concurrent hyperlipidemia, hypertension and diabetes mellitus as coexistent diseases were present in 9 (10.7%), 54 (64.3%) and 17 (20.2%) of the included patients, respectively. NRS score change from day one to day thirty was significantly different between pre-treatment (6.7 ± 2.51) and post-treatment (3.4 ± 3.01), (CI 0.442-1.962, $p = 0.002$).

Comparing patients with adequate and inadequate responses

Our results found that 50 patients (59.5%) showed a clinically significant improvement according to NRS scores (≥ 3 points decline in post-treatment NRS). In the second step of our analysis we tried to find probable effects of patients` demographics and clinical characteristics on their response to the suggested regimen.

Our findings revealed that distribution of gender, age category, previous history of diabetes mellitus; hypertension; hyperlipidemia, and stroke-type were not statistically different between the responders and non-responders. These findings are presented in Table 1.

Discussion

In this multicenter study we showed that in more than half of patients with central post stroke pain, the NRS pain score was reduced after a month of therapeutic course with gabapentin.

For patients with thalamic syndrome due to severity and chronicity, like other types of chronic pain, reduction of pain intensity, instead of pain elimination, should be considered as the goal of the treatment strategy. Hence, in the present study and in order to perform a better evaluation of pain intensity we used NRS. By NRS, patients will be asked about their pain and this individualized scoring can help physician make a better assessment.

Central pain syndrome is a neurological condition that originates from damage to the central nervous system (CNS) or may happen due to impairment of the function of CNS. Many conditions such as stroke, tumors of CNS and spinal cord, multiple sclerosis, epilepsy, brain or spinal cord trauma or can be served as an underlying process and induce this pain syndrome.

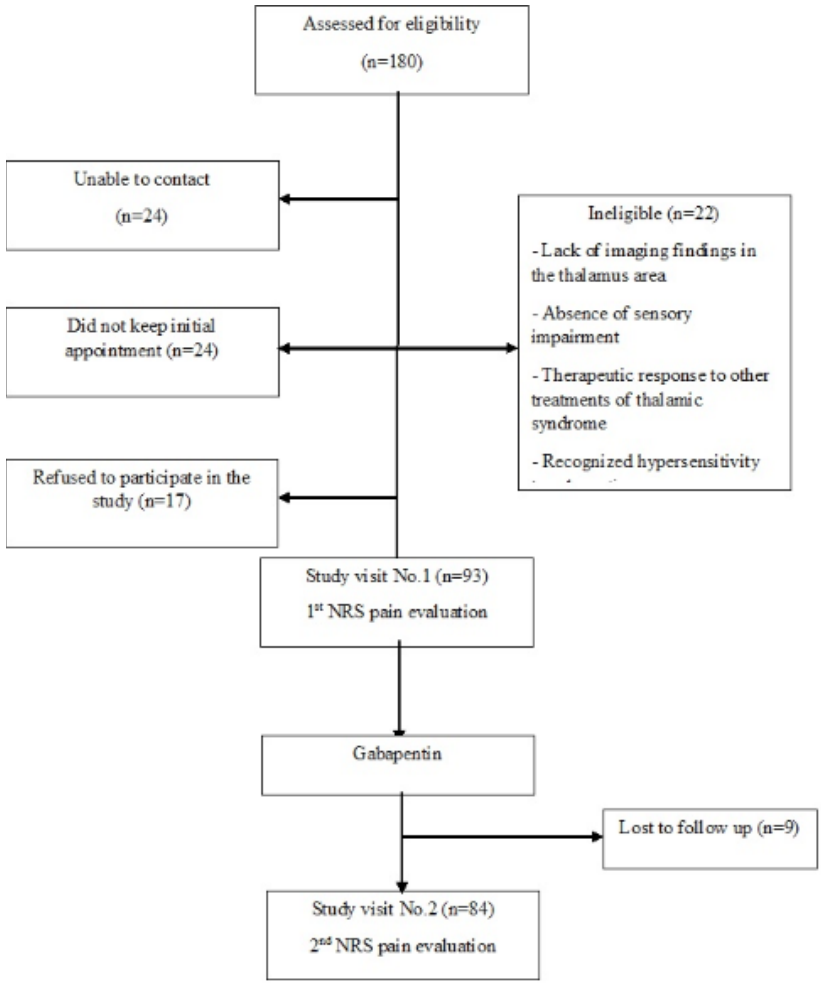

Figure 1. Flowchart of the study; NRS, Numeric Rating Scale.

The probable pathophysiology of thalamic syndrome includes a post-stroke lesion of thalamus that results in toxic, anatomical and inflammatory changes which simultaneously ruins the inhibitory mechanisms of the sensory thalamus and its related neuronal pathways and also can destruct the afforestation of the sensory pathways and eventually results in neuronal hyper excitability above the level of differentiation (18-20). This hyperactivity can result in central sensitization, which in turn leads to chronic pain (21).

The diversity and convolution of damages affected multiple parts of the spinothalamocortical pathway, indicates the intricate pathophysiology of this pain and clarifies the challenge of its effective treatment.

Gabapentin (Neurontin), 1–(aminomethyl) cyclohexane–acetic acid, is an antiseizure drug primarily approved for treatment of partial seizures with an undocumented mechanism of action, however recent studies have reported that probably gabapentin elevates gamma-Aminobutyric acid (GABA) levels in the different parts of the brain including the thalamus as well as inducing GABA release from glial cells. Although, the action sites of gabapentin for pain reduction has not been well clarified but both animal (22-24) and human (25) studies have shown both spinal and supraspinal sites of action.

Several reports have been demonstrated gabapentin as a first line treatment (26-28) or as an add-on therapy in combination with other drugs (29) in patients suffering from

Table 1. Demographic and clinical characteristics of patients and their effect on therapeutic response with gabapentin.

Characteristics	Responders	Non-responders	Total	p-value
Gender				
Male	25(29.7%)	19(22.6%)	44(52.4%)	N.S
Female	25(29.7%)	15(17.8%)	40(47.6%)	N.S
Age groups				N.S
<40	3(3.5%)	1(1.1%)	4(4.8%)	
41-50	6(7.1%)	6(7.1%)	12(14.3%)	
51-60	15(17.8%)	11(13%)	26(31%)	
61-70	17(20.2%)	12(14.2%)	29(34.5%)	
>70	9(10.7%)	4(4.7%)	13(15.5%)	
Underlying disease				
Hyperlipidemia	6(7.1%)	3(3.5%)	9(10.7%)	N.S
Hypertension	36(42.8%)	18(21.4%)	54(64.3%)	N.S
Diabetes mellitus	11(13%)	6(7.1%)	17(20.2%)	N.S
Type of stroke				
Hemorrhagic	7(8.3%)	1(1.1%)	8(9.5%)	N.S
Ischemic	43(51.1%)	33(39.2%)	76(90.5%)	N.S

peripheral neuropathic pains such as post-herpetic neuralgia, sciatic type pain and diabetic neuralgia. This is while specific research on gabapentin to treat central pains is limited to case series and low quality clinical trials. So far, gabapentin has been shown to be efficacious in relieving the spontaneous and paroxysmal pain caused by peripheral and central lesions (30).

In a case report published by Chen *et al*. (8), gabapentin was suggested as an effective and well-tolerated drug for a patient with central post-stroke pain syndrome who failed to respond to a variety of oral analgesics.

Similarly, in our study all of the patients tolerated the drug well and no one discontinued the therapeutic course because of the adverse events of the drug.

Previously, gabapentin has been shown as an effective second line medication to decrease the pain intensity in cases who failed to achieve a proper response after standard treatment with first line agents like lamotrigine and amitriptyline (4).

Amitriptyline, from the antidepressants group, was among the first drugs proven to be effective in central post stroke pain syndrome in a double-blind placebo-controlled study (31). Lamotrigine, as an anti-epileptic medication with non-NMDA anti-glutamatergic activity, has been proposed as an alternative to tricyclic antidepressants in the treatment of central post stroke pain. Analgesic abilities of lamotrigine in reduction of both the spontaneous and evoked components of central pains have been evaluated in a case series and its efficacy has been proven (32).

Due to possible dose dependent adverse effects of gabapentin, this study tried low doses of this drug. In our study, the proposed daily dosage of 600 mg yielded a significant clinical improvement with no adverse effects. Serpell and colleagues have evaluated clinical efficacy of higher doses of gabapentin titrated to 2400 mg/day in 9 patients with central post stroke pain over an eight weeks period (17). Clinical outcomes of that study are comparable to the findings of the present study but we achieved our results with a very lower dosage. Safety and efficacy of gabapentin with a limited dose makes this agent a superior therapeutic option in comparison with conventional analgesics.

Usual analgesics, including opioids, are generally ineffective in treatment of central post stroke pain and due to their possible adverse events; it is generally recommended that they should be avoided. In a study published by Attal *et al.* (33), there was no significant difference between the effects of morphine and placebo.

In that study, only a minority of patients got benefit from long-term treatment with opioids. Moreover, the use of opioids as oral agents in pain reduction in patients with central and peripheral neuropathic pain has been trialed in a study by Rowbotham *et al.* (34). The study demonstrated that patients with central pain, compared with those with peripheral neuropathic pain, were less likely to obtain benefits.

We also attempted to determine the probable influence of baseline characteristics on the therapeutic response, and found that baseline type of stroke, age, gender, positive history for hyperlipidemia; hypertension and diabetes mellitus did not have a statistically significant effect on response to treatment. Further baseline characteristics analyses are needed to help identify probable gabapentin response factors.

In conclusion, the findings of this study show gabapentin as an effective and well tolerable treatment for patients with thalamic syndrome. There is a paucity of data toward the efficacy of this drug in pain relief in patients with thalamic syndrome, so we suggest more clinical trials to be conducted to evaluate various aspects of using gabapentin in treating patients with thalamic syndrome. Given the safety and lack of interaction with other drugs we suggest gabapentin to be considered as a first line therapy or as add-on therapy for reducing the pain severity in patients with thalamic syndrome. A randomized controlled trial with a larger sample size may attenuate methodological weaknesses of the present trial and open new avenues for a successful usage of gabapentin in these patients.

References

(1) Klit H, Finnerup NB and Jensen TS. Central post-stroke pain: clinical characteristics, pathophysiology, and management. *Lancet Neurol.* (2009) 8: 857-868.

(2) Klit H, Finnerup NB, Andersen G and Jensen TS. Central poststroke pain: a population-based study. *Pain* (2011) 152: 818-824.

(3) Cepeda MS, Africano JM, Polo R, Alcala R and Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* (2003) 105: 151-157.

(4) Kumar B, Kalita J, Kumar G and Misra UK. Central poststroke pain: a review of pathophysiology and treatment. *Anesth. Analg.* (2009) 108: 1645-1657.

(5) Harvey RL. Central poststroke pain syndrome. *Top Stroke Rehabil.* (2010) 17: 163-172.

(6) Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T and European Federation of Neurological S. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur. J. Neurol.* (2010) 17: 1113-1188.

(7) Frese A, Husstedt IW, Ringelstein EB and Evers S. Pharmacologic treatment of central post-stroke pain. *Clin. J. Pain.* (2006) 22: 252-260.

(8) Chen B, Stitik TP, Foye PM, Nadler SF and DeLisa JA. Central post-stroke pain syndrome: yet another use for gabapentin? *Am. J. Phys. Med. Rehabil.* (2002) 81: 718-720.

(9) Ueda K, Namiki T, Kasahara Y, Chino A, Okamoto H, Ogawa K and Terasawa K. A case of thalamic pain successfully treated with Kampo medicine. *J. Altern. Complement Med.* (2011) 17: 567-570.

(10) Ramachandran VS, McGeoch PD and Williams L. Can vestibular caloric stimulation be used to treat Dejerine-Roussy syndrome? *Med. Hypotheses* (2007) 69: 486-488.

(11) Dworkin RH, O›Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC and Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* (2007) 132: 237-251.

(12) Finnerup NB, Otto M, McQuay HJ, Jensen TS and Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain.* (2005) 118: 289-305.

(13) Behnam B, Semnani V, Saghafi N, Ghorbani R, Shori MD and Choobmasjedi SG. Gabapentin effect on pain associated with heroin withdrawal in iranian crack: a randomized double-blind clinical trial. *Iran. J. Pharm. Res.* (2012) 11: 979-983.

(14) Keyhanfar F, Shamsi Meymandi M, Sepehri G, Rastegaryanzadeh R and Heravi G. Evaluation of antinociceptive effect of pregabalin in mice and its combination with tramadol using tail flick test. *Iran. J. Pharm. Res.* (2013) 12: 483-493.

(15) Daily Med, Current Medication Information. Updated periodically, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894.

(16) Moore RA, Wiffen PJ, Derry S and McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst. Rev.* (2011) 16.

(17) Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. *Pain.* (2002) 99: 557-566.

(18) Nicholson BD. Evaluation and treatment of central pain syndromes. *Neurol.* (2004) 62: 30-36.

(19) Yezierski RP. Spinal cord injury: a model of central neuropathic pain. *Neurosignals* (2005) 14: 182-193.

(20) Bowsher D. Stroke and central poststroke pain in an elderly population. *J. Pain.* (2001) 2: 258-261.

(21) Finnerup NB. A review of central neuropathic pain states. *Curr .Opin. Anaesthesiol.* (2008) 21: 586-589.

(22) Partridge BJ, Chaplan SR, Sakamoto E and Yaksh TL. Characterization of the effects of gabapentin and 3-isobutyl-gamma-aminobutyric acid on substance P-induced thermal hyperalgesia. *Anesthesiol.* (1998) 88: 196-205.
(23) Takeuchi Y, Takasu K, Ono H and Tanabe M. Pregabalin, S-(+)-3-isobutylgaba, activates the descending noradrenergic system to alleviate neuropathic pain in the mouse partial sciatic nerve ligation model. *Neuropharmacol.* (2007) 53: 842-853.
(24) Tanabe M, Ono K, Honda M and Ono H. Gabapentin and pregabalin ameliorate mechanical hypersensitivity after spinal cord injury in mice. *Eur. J. Pharmacol.* (2009) 609: 65-68.
(25) Hayashida K, DeGoes S, Curry R and Eisenach JC. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. *Anesthesiol.* (2007) 106: 557-562.
(26) Chogtu B, Bairy KL, Smitha D, Dhar S and Himabindu P. Comparison of the efficacy of carbamazepine, gabapentin and lamotrigine for neuropathic pain in rats. *Indian J. Pharmacol.* (2011) 43: 596-598.
(27) Hyatt JD, Daniel D, Tran QV, Millares M and Kubota DR. Diabetic peripheral neuropathic pain: is gabapentin effective? *Am. Fam. Physician* (2011) 84: 480.
(28) Chou R. ACP Journal Club. Review: Gabapentin reduces some types of chronic neuropathic pain more than placebo in adults. *Ann. Intern. Med.* (2011) 155: 1-8.
(29) Vorobeychik Y, Gordin V, Mao J and Chen L. Combination therapy for neuropathic pain: a review of current evidence. *CNS Drugs* (2011) 25: 1023-1034.
(30) Attal N, Brasseur L, Parker F, Chauvin M and Bouhassira D. Effects of gabapentin on the different components of peripheral and central neuropathic pain syndromes: a pilot study. *Eur. Neurol.* (1998) 40: 191-200.
(31) Leijon G and Boivie J. Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine. *Pain.* (1989) 36: 27-36.
(32) Canavero S and Bonicalzi V. Lamotrigine control of central pain. *Pain.* (1996) 68: 179-181.
(33) Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M and Bouhassira D. Effects of IV morphine in central pain: a randomized placebo-controlled study. *Neurol.* (2002) 58: 554-563.
(34) Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K and Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl. J. Med.* (2003) 348: 1223-1232.

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