Comparative Study of Clinical Efficacy of Amitriptyline and Pregabalin in Postherpetic Neuralgia

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Summary: The most common complication of herpes zoster in immunocompetent patients is postherpetic neuralgia, which is very difficult to treat. Significant beneficial effects have been found for amitriptyline, gabapentin, pregabalin, carbamazepine, sodium valproate, oxycodone, corticosteroid, topical capsaicin, tramadol, etc. The aim of this open randomized comparative study was to demonstrate clinical efficacy of amitriptyline and pregabalin. The study included 50 patients, 32 (64%) male and 18 (36%) female, randomized to receive either amitriptyline or pregabalin (n=25 each). Amitriptyline was administered in a dose of 25 mg once daily and pregabalin in a dose of 75 mg twice daily. Inclusion criteria were as follows: postherpetic neuralgia of more than 1 month duration; pain of at least moderate severity; and patient age 40 years or older and no pregnancy. Patients with a history of any serious diseases (renal, cardiac, hepatic or seizure) were excluded. Total treatment period spanned 8 weeks, with patient follow up visits at 2, 4 and 8 weeks to assess the degree of improvement in pain perception and any adverse reaction. Patients with four herpes zoster types were included in this study, of which thoracic type predominated (54%). Other types were cervical in 12 (24%), trigeminal in 8 (16%) and lumbosacral in 3 (6%) patients. Prodromal symptoms before herpes zoster were reported by 66% of study patients. Satisfactory improvements of pain perception at the end of 8 weeks (>75%) were noticed in pregabalin group, which was statistically significant ($\chi^2=10.08; P<0.05$). Dry mouth was the commonest complication in amitriptyline group and dizziness in pregabalin group. More importantly, none of the patients stopped treatment due to adverse reaction. In conclusion, therapy with pregabalin is better compared to amitriptyline in postherpetic neuralgia patients. However, a similar study in a larger sample is required to validate the present findings.

Key Words: amitriptyline, herpes zoster, pregabalin, postherpetic neuralgia
INTRODUCTION

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, which results from a combination of inflammatory and viral damage to primary afferent fibers of sensory nerve. Herpes zoster is initially characterized by a prodromal phase that is associated with pain and paresthesia in the affected dermatome. An hour to days later, maculopapular eruption appears and progresses to vesicles, then pustules and finally crusts, and heals 3-4 weeks later. In some patients, pain may persist weeks to months or years after the skin lesion healed, hence the term postherpetic neuralgia. There are three phases of PHN: acute, subacute and chronic (1).

The acute phase occurs with the onset of rash and lasts for approximately 30 days; subacute phase lasts for 1-3 months after the onset of rash; and chronic phase or PHN lasts for 3 months or more after the onset of rash (2). The exact point at which acute herpes becomes PHN is arbitrary. Duration of PHN has been evaluated by using two definitions: pain persisting after healing of rash and pain persisting for more than 30 days after the development of rash (3). Some authors also described PHN as pain persisting for at least 3 months after rash healing (1,4). As the definition of PHN varies according to the defined period of pain persistence after resolution of rash, the actual incidence remains unknown. Approximately 1 million cases of herpes zoster occur in the United States of America per year and this incidence can likely increase with population aging (5). It is estimated that 9%-34% of herpes zoster patients develop PHN (4). Approximately 80%-85% of PHN cases develop in herpes zoster patients aged over 50 (6). Advanced age, increased severity of acute pain, greater extends of rash, and presence of prodromal symptoms will increase PHN development and severity (50%-75% have persisting pain six months after rash) (6,7).

Pain of PHN may persist for weeks, months or even years. The pain has been described as mild to excruciating in severity, constant, intermittent, lasting from few minutes to being constant daily or almost daily (8). The pain can be constant, deep, burning with an intermittent sharp stabbing, shooting in nature. These patients may also have allodynia, may be unable to have clothing in the area of allodynia and thus dressing, bathing are grooming, and mobility may be effected (9). PHN patients can experience chronic fatigue, anorexia, weight loss and depression. Their social role may change from an active person in the community to an individual who rarely leaves home. It has been described as one of the most common causes of pain related suicide in the elderly (10).

Pathophysiologically, there are two different mechanisms; sensitization and deafferentation can explain PHN pain (11). Two types of sensitization are present, peripheral and central. Peripheral sensitization: subsequent to tissue injury, nociceptors become sensitized, resulting in spontaneous discharge activity and hyperexcitability. Central sensitization: exacerbation of dorsal horn neuron response to afferent stimuli and expansion of their receptive fields by prolonged nociceptor discharge may lead to allodynia without sensory loss. Deafferentation pain: reactivation of the varicella zoster virus results in neural damage and inflammation with subsequent edema. Other mechanisms of PHN pain include neuronal formation or neuronal sprouting and local axons reinnervating previously denervated area (12).

The goal of therapy for PHN is to reduce patient morbidity. No treatment has been shown to completely prevent, yet some treatments may shorten the duration or lessen the severity of symptoms. Among different treatments, antiviral, antidepressants, anticonvulsants, anesthetics, analgesics and corticosteroids have been used. A recently approved vaccine is also effective in preventing PHN (13). Recent trials demonstrated the combinations of gabapentin with nortriptyline and pregabalin with amitriptyline to be more efficacious than either drug as monotherapy (14,15).

More than one mechanism of action of PHN seems to be involved and many patients are refractory to different treatments. Because of inadequate pain relief and intolerable side effects, some patients stopped treatment during therapy. The aim of our study was to assess comparative clinical efficacy of amitriptyline and pregabalin in PHN patients.

PATIENTS AND METHODS

This open randomized comparative study of clinical efficacy was carried out in Midnapore Medical College Skin OPD with amitriptyline and pregabalin administered to PHN patients during the period from April 2008 to March 2009. Inclusion criteria were as follows: (i) PHN of more that 1 month duration; (ii) pain of at least moderate severity, bothersome, disagreeable and unpleasant; and (iii) patients aged ≥40 years. PHN patients with cardiac disease, seizure disorder, severe depression with suicidal intent requiring urgent management, other significant pain problem, previous history of brain damage caused by head injury or stroke were excluded.

The study included 50 patients randomized into two groups of 25 patients to receive 25 mg amitriptyline daily at night or 75 mg pregabalin twice daily. The
two medicines were allocated upon randomization with every odd number for amitriptyline and even number for pregabalin. It is important to note that there were no analgesics provided to study patients during the study period. A written informed consent was obtained from each patient at enrolment. General physical and neurologic as well as other systematic examinations were done prior to treatment initiation. The institutional ethics committee approved the study protocol prior to starting therapy.

Total study period was 8 weeks and patients were assessed on follow up at 2, 4 and 8 weeks to observe the degree of improvement of pain perception and any adverse drug reaction.

The initial dose of amitriptyline was 10 mg daily, increased to 25 mg daily after 5 days. The initial dose of pregabalin was 75 mg once daily, increased to 75 mg twice daily in 5 days.

A visual analogue scale (VAS) was used to evaluate steady pain, brief lancinating or paroxysmal pain and allodynia by touching the skin. The categorical scale used the words “no pain”, “mild” (present but not bothering, once), “moderate” (bothersome, disagreeable and unpleasant), “severe” (unbearable), and “very severe” (requiring bed rest). An improvement of categorical scale was a change from moderate or severe to a lesser category. Pain relief was assessed with a percentage rating, with patient being asked to estimate from 0 to 100%, how much better it was. We considered 50% improvement as satisfactory improvement after 4 weeks of treatment and 75% improvement as satisfactory after 8 weeks of treatment. A check list of side effects was recorded on each visit and if some side effect was present, the patients were asked whether it was tolerable or intolerable.

**Statistical analysis**

Differences in clinical efficacy between the two groups were compared using $\chi^2$-test. Odds ratio and 95% confidence interval was calculated by standard methods. All statistical analyses were performed using MedCalc statistical software (Version 11.4, MedCalc Software bvba). The level of statistical significance was set at $P<0.05$.

**RESULTS**

A total of PHN 50 patients were included in the study. The patients were divided into two groups receiving amitriptyline and pregabalin (n=25 each). All study patients completed the 8-week study period except for 3 patients in pregabalin group and 4 patients in amitriptyline group, where there was no or very little improvement. We received this information about their reason to stop treatment from these patients by telephone.

Out of total 50 patients, 32 (64%) were male and 18 (36%) female (Table 1). Four types of PHN were present in study patients, predominated by the thoracic type in 27/50 patients (54%). Other types were trigeminal in 16% (8/50), cervical in 24% (12/50) and lumbar in 6% (3/50) of patients. A history of prodromal symptoms was reported by 26% (33/50) of our patients.

Comparative assessments of pain perception were noted during the study period. Satisfactory

| Table 1. Patient characteristics in comparative study of clinical efficacy of examined drugs |
|-----------------------------------------------|-----------------|-----------------|
|                                               | Amitriptyline   | Pregabalin      |
|                                               | (n=25)          | (n=25)          |
| **Sex**                                       |                 |                 |
| Male                                          | 16              | 16              |
| Female                                        | 9               | 9               |
| **Distribution**                              |                 |                 |
| Thoracic                                      | 17              | 10              |
| Trigeminal                                    | 2               | 6               |
| Cervical                                      | 5               | 7               |
| Lumbar                                        | 1               | 2               |
| **Presence of prodromal symptom**             | 18              | 15              |

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improvement was considered if 50% improvement of pain perception was observed after 4 weeks of treatment (Table 2). It was noticed that improvement was 1.2 times greater (OR=1.19; 95%CI 0.32-4.34) in amitriptyline group as compared with pregabalin group. However, this difference in satisfactory improvement between the two groups was not statistically significant ($\chi^2$-test=0.09; $P>0.05$).

At the end of 8 weeks, more than 75% improvement of pain perception was considered to be satisfactory (Table 3). A statistically significant difference of improvement was noticed in pregabalin group ($\chi^2$-test=10.083; $P=0.0015$). Satisfactory improvement was reported by only 16% of 25 amitriptyline group patients versus 64% of 25 pregabalin group patients. In pregabalin group, the rate of improvement was more than 9-fold (OR=9.33; 95%CI 2.43-35.84) of that found in amitriptyline group.

Dryness of the mouth was the commonest side effect of amitriptyline group (12/25) and dizziness in pregabalin group (9/25). More importantly, in pregabalin group the rate of side effects was 1.6 times lower (OR=1.64; 95%CI 0.46-5.97) than in amitriptyline group. The intensity of adverse reaction was mild to moderate and none of the patients discontinued treatment due to side effects.

DISCUSSION

The present study demonstrated pregabalin to be more efficacious than amitriptyline in relieving pain at the end of 8-week treatment but there was no statistically significant difference in terms of satisfactory improvement in either group after 4 weeks of treatment. A recent study has suggested that long-term treatment with pregabalin may be beneficial in patients with PHN (16). Various studies with amitriptyline, nortriptyline or desipramine versus placebo showed significant benefits associated with antidepressant therapy (17,18).

Gabapentin, an anticonvulsant, has been used in neuropathic pain. In a multicenter, randomized, double blind, placebo controlled, parallel design, 8-week trial, gabapentin significantly reduced PHN pain (reduction in the mean daily pain score from 6.3 to 4.2 on gabapentin vs. reduction from 6.5 to 6 on placebo) and associated sleep disturbance with an improvement in mood and quality of life (19). Pregabalin, an anticonvulsant, has also been used to treat neuropathic pain. In a multicenter, parallel group, double blind, placebo controlled 8-week randomized clinical trial, pregabalin significantly reduced postherpetic pain (20).

There were some comparative studies demonstrating differences in clinical efficacy with one drug versus another drug. A randomized, double blind, crossover study with amitriptyline versus maprotiline was published in 1992. The results revealed that amitriptyline was associated with 50% pain reduction in 47% (15/32) and maprotiline in 38% (12/32) of patients but there was no statistically significant difference between the two drug groups (21). In another study, amitriptyline and nortriptyline were equally effective with approximately 50% achieving good response (22). A comparative double blind parallel group study compared gabapentin and nortriptyline in PHN patients. Results showed that both medicines were almost equally effective but gabapentin was better tolerated compared to nortriptyline (23). Results of a comparative study with gabapentin and pregabalin in PHN patients showed that analgesic action of pregabalin was six times that of gabapentin in terms of effectiveness in dose conversion. Pain reduction can also be expected with increasing the dose of pregabalin, with close observation for any significant adverse effects (24). Another two studies published in 2009 and 2010 found combination therapy with two different groups of drugs to be more effective than single drugs. Combined therapy with gabapentin and nortriptyline was more effective than either drug given alone for neuropathic pain, therefore the authors recommended using this combination in patients showing partial response to either drug given alone and seeking additional pain relief (15). Combination therapies with amitriptyline and pregabalin were better to relieve pain perception in PHN patients (15).
Like the present study, earlier studies also observed that dizziness was the commonest adverse effect in pregabalin treated patients (16,20). Pooled analysis of patients treated with amitriptyline showed 84% of participants to report minor adverse events, with 13%-74% of patients reporting dry mouth. We also found dryness of the mouth to be most frequently reported (48%) in amitriptyline group.

**CONCLUSION**

To our knowledge, clinical efficacy of pregabalin and amitriptyline has not yet been compared in any previous study. Although the sample size was small, we found a clinically significantly better response with pregabalin compared to amitriptyline; however, a large number of patients are required to make definite conclusions.

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**References**


