A study on efficacy of Pregabalin in acute Herpetic Neuralgia

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KEY WORDS

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ABSTRACT

Background: Herpes zoster is an intractable painful condition. The pain during first thirty days of onset is known as acute herpetic neuralgia. Multiple treatments using NSAIDS, opioids and tricyclic antidepressants are available but the role of pregabalin in acute Herpetic Neuralgia is not assessed in any of Indian studies. **Purpose**: This study was aimed to determine efficacy and safety of Pregabalin in reducing pain of acute Herpetic Neuralgia. **Methods:** In this placebo-controlled 4 week trial including 45 subjects, 23 patients received Pregabalin in the dosage of 150 mg/day in divided doses and 22 patients received placebo within 72 hours of onset of Herpes zoster. **Results:** Subjects receiving Pregabalin had a statistically significant reduction ($p<0.0001$) in visual analogue scale(VAS) score as compared to placebo, indicating the efficacy of Pregabalin in the treatment of acute pain associated with Herpes zoster. Side effects most commonly noted were somnolence and dizziness. **Conclusion:** The results of this study indicate that Pregabalin is effective in relieving pain of acute Herpetic Neuralgia.

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Introduction

Acute Herpetic Neuralgia is characterized by burning, aching, electric shock like pain, or unbearable itching in association with the outbreak of herpes zoster rash.[1] The pain is associated with dysesthesias, paresthesias, hyperalgesia, hyperesthesia with allodynia (production of pain by innocuous stimuli) and the severity of zoster increases with age.[2] The International Herpes Management Forum (IHMF®) defines "Acute Herpetic Neuralgia" as the pain from onset of prodrome to 30 days; pain between 30 days from prodrome onset to 4 months is "Subacute Herpetic Neuralgia" and pain persisting beyond 4 months from onset of the prodrome of Herpes zoster is "Post Herpetic Neuralgia".[3]

There are multiple studies on management of PHN but little has been explored on acute Herpetic Neuralgia. Conventionally, the treatments used for pain alleviation in acute Herpetic Neuralgia are NSAIDS, oxycodone and morphine etc. having variable efficacy.[4] There are studies with certain other drugs like amitryptyline and nortryptyline, but these drugs, even though being effective, have more disturbing side effects.[5]

Pregabalin is used for various neuropathic painful conditions.[6,7] However, its role in acute pain of zoster has not been explored. This study was done to evaluate the efficacy and safety of Pregabalin in patients with acute Herpetic Neuralgia.

Methods

The study was done between May 2009 to April 2011, including patients with acute Herpes zoster presenting within 72 hours of onset, having pain rating 50 or above at baseline on 100mm linear Visual Analogue Scale(VAS). This study was a double blind controlled trial. The subjects were controlled for age and sex. They were assigned into two groups to receive Pregabalin 150mg/day and placebo. At each visit (weeks 0, 1, 2, 3 and 4) subjects were assessed for pain on 100-mm Linear VAS and adverse events were recorded. Eligible subjects who gave informed written consent underwent physical examination. Blood samples were taken for routine hematology and chemistry. Medical histories and demographics were obtained. Oral acyclovir 800mg was given 5 times per day for 7 days to all patients of herpes zoster. The study was approved from the Institutional ethical committee.

Exclusion criteria included the following patients: Acute Herpes zoster presenting after 72 hours of onset; pain of Herpes zoster rating less than 50 at baseline; prior treatment with Pregabalin; history of hypersensitivity to the drug or its ingredients; significant hematological derangements; immunocompromised state; significant systemic disease or hepatic and renal disease.

Statistical analysis

For statistical analysis two-Sample Independent "*t*" test and "Hartley's *f* test" for equality of variance was applied by using Epi Info software for the comparison of the safety and efficacy of Pregabalin with placebo. Probability value of less than 0.05 ($p<0.05$) was considered statistically significant.

Results

A total of 237 patients visited the Dermatology clinic for Herpes zoster during the study period. Of these, 45 patients were eligible for the study according to inclusion and exclusion criteria. The disease characteristic of the patients showed that the most common area of localization was thoracic followed by lumbar region. The mean time since zoster onset was ranging from 49-51 hours and the mean VAS score was between 81-83 at first visit (Table 1).

Pain assessment in patients by VAS showed continuous decrease VAS in Pregabalin treated group till 4th week (Table 2). Change in VAS was highly significant ($p<0.001$) as compared with placebo by using two sample independent "*t*" test and "Hartley's *f* test" for equality of variance (Table 3).

Safety and adverse effects

Most frequently reported adverse effects were somnolence (mean = 26.97%), dizziness (mean = 14.95%) and gastrointestinal (mean = 6.49%) in patients receiving Pregabalin 150 mg/day. The adverse effects were higher in frequency and intensity in first two weeks of therapy and thereafter were reduced in 3rd to 4th week (Table 4).

Table 1: Demographic and disease characteristic of the patients

Characteristics		Oral pregabalin 150 mg (n = 23)	Placebo (n = 22)	p value
Sex	Male	19(82.60%)	17(77.27%)	N.S.*
	Female	4(17.39%)	5(22.72%)	
Age (in years)	Mean	46	47	N.S.
	Range	31-57	29-58	
Localization	Trigeminal	2(8.69%)	2(9.09%)	N.S.
	Cervical	1(4.34%)	1(4.54%)	
	Thoracic	16(69.56%)	16(72.72%)	
	Lumbar	4(17.39%)	3(13.63%)	
Mean time since zoster (in hours)		49	51	N.S.
Mean Base line VAS score (pain)		83	81	N.S.

* Non Significant

Table 2: Summary of average (mean) pain score on 100 mm linear visual analogue scale

Drug dosage	Mean VAS score					S.D.* at 4th week
	Week 0	End of 1st week	End of 2nd week	End of 3rd week	End of 4th week	
Placebo	81	82	76	74	74	3.03
Pregabalin (150mg/day)	82	78	65	52	53	5.85

*Standard deviation

Table 3: Results of Two-Sample Independent "*t*" Test between pregabalin treated and placebo groups after 4 weeks

Result	*t* statistics	*df*	p-value*	Mean Difference	Lower Limit	Upper Limit
Equal variance	−15.016	43	<0.0000001	−21	−23.82	−18.18
Unequal variance	−15.214	33	<0.0000001	−21	−23.808	−18.19
	***F* statistics**		***df(degree of freedom)* (numerator,denominator)**		**p-value***	
Test for equality of variance†	3.72758		22,21		0.003737	

* p-value (two-tailed),
† Hartley's *f* test for equality of variance

Table 4: Adverse effects in patients administered pregabalin 150 mg/day

Adverse effect		Week 1	Week 2	Week 3	Week 4
Somnolence		38.5%	31.4%	21.5%	16.5%
Dizziness		19.4%	16.5%	12.4%	11.5%
Gastro-intestinal	Dry mouth	14.5%	12.5%	7.5%	4.5%
	Constipation	9.5%	8.7%	5.6%	3.5%
	Diarrhoea	4.8%	3.2%	2.4%	1.5%

Discussion

Acute herpetic neuralgia is a painful condition which is almost always experienced by patients suffering from herpes zoster and is much more common than post herpetic neuralgia.[2] Pregabalin is a calcium channel alpha-2δ ligand with analgesic, anxiolytic, and anticonvulsant properties that acts both centrally and peripherally.[8] Pregabalin has been studied for the cases of post herpetic neuralgia and the drug has shown promising results.[6,9,10] But the role of Pregabalin has not been studied for sustained relief of pain in acute Herpetic Neuralgia.

In the present study, Pregabalin was administered for 4 weeks, and pain was assessed on VAS and was analyzed every week. Pregabalin showed significantly better response in comparison to placebo ($p<0.0001$). The effect was manifested as early as at the end of first week and the optimum response was observed at the end of second week, which continued till the end of therapy.

The only report available for the effective use of Pregabalin in acute Herpetic Neuralgia with single oral dose of 150 mg is by Jensen-dahm *et al*.[11] In the above mentioned study which enrolled 8 patients without any controls, the observation period was for 6 hours. In this study reduction of pain was 33% at the end of 6 hours. In the present study which included 23 patients (with 22 controls), the patients were kept under surveillance for a period of 4 weeks. The reduction in pain perception was 55.42% at the end of 4th week of therapy. The results indicate that repeat daily administration of Pregabalin is more effective as compared to single stat dose administration. The reason for better response in our study could be due to sustained level of drug for 4 weeks, leading to steady reduction in pain.

The adverse effects observed include somnolence, dizziness and gastrointestinal disturbance. None of these was severe or serious enough to call for discontinuation of the drug. Patients tolerated the reactions without much discomfort. In studies where Pregabalin was used for post Herpetic Neuralgia in a dose of 600 mg or more, the adverse reactions were higher.[6,9,10] These ranged from high percentage of somnolence, dizziness and ataxia as compared to present study. The fewer side effects in the present study could be assigned to smaller amount of drug used i.e. 150 mg per day. This can also be explained by linear gastrointestinal absorption and minimal metabolization of the drug with no known drug-drug interactions and is excreted unchanged from the kidneys.[8]

The study shows that Pregabalin is efficacious with safe profile in the dose of 150 mg/day in acute Herpetic Neuralgia.

The article complies with International Committee of Medical Journal Editor's uniform requirements for the manuscripts.

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