Original Article

Safety and Efficacy of Different Systemic Treatment Modalities for Acute Pain of Herpes Zoster: A Pilot Study

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Abstract

Background: Herpes zoster is a viral infection of skin caused by Varicella Zoster virus. The most important symptom for which the patient seeks medical advice is pain, which is perceived before the development of rash and lasts even after its resolution. The pain during the first 30 days after onset of herpes zoster is known as acute herpetic neuralgia. The aim of this study was to compare the efficacy and side-effects of different systemic treatment modalities for acute herpes zoster neuralgia. **Materials and Methods:** This was a randomized, single-blind, parallel control study. Forty-five patients of herpes zoster within 72 hours of onset were enrolled after considering various inclusion and exclusion criteria over a duration of 1 year. Pain severity was assessed after sequential distribution and allotment of patients in three groups using verbal rating scale (VRS). Patients in Group A (control group), were treated with Tab.valacyclovir (1 g tds × 7 days), Group B–Tab.valacyclovir (1 g tds × 7 days) + Cap. Pregabalin (75 mg bd × 1 month), and Group C –Tab.valacyclovir (1 g tds × 7 days) +Cap. Pregabalin (75 mg bd × 1 month) + Tab.methylprednisolone (0.64 mg/kg body weight in two divided doses × 7 days). Patients were followed up at 1, 4, 6 weeks. Complete resolution of acute pain and side-effects were noted. **Results:** At the end of 4 weeks, reduction in acute pain was statistically significant ($P < 0.05$) in all the three groups individually compared to the baseline value. At the end of 6 weeks, percentage of patients with persistence of pain was more in Group A and B compared to Group C, which was statistically significant ($P = 0.0001$). In group A, postherpetic neuralgia was observed in more patients compared to group B and C. No significant side-effects were observed in any group except vomiting, somnolence, and dizziness. **Limitations:** Sample size of this study was limited. Further studies with large sample size are required to further validate the findings of the present study. **Conclusions:** Combination therapy with valacyclovir, methylprednisolone, and pregabalin has better efficacy compared to valacyclovir and pregabalin and valacyclovir alone in the management of acute herpes zoster neuralgia. No significant side-effects were observed

Keywords: *Acute herpes zoster pain, methylprednisolone, pregabalin, valacyclovir*

Introduction

Herpes zoster is a viral infection of the skin caused by Varicella Zoster virus. The most important symptom for which patients seek medical advice is pain, which is perceived before the development of rash and lasts even after its resolution. The pain during the first 30 days after onset of herpes zoster is known as acute herpetic neuralgia. The results of considerable number of recent prospective studies have demonstrated that, more the severity of acute pain, greater is the risk of developing postherpetic neuralgia (PHN). There is paucity of studies regarding the management of acute herpes zoster neuralgia. With this background, this study was designed to target the disease in its initial stage using potent antiviral drug alone and in combination with anti-inflammatory and other pain relieving drugs to evaluate their effect on acute herpetic neuralgia.

Aim and objectives of the study were (1) to compare the efficacy of valacyclovir with pregabalin and valacyclovir, pregabalin, and methylprednisolone and valacyclovir alone in acute herpetic neuralgia; (2) to study the side-effects associated with these combination therapies.

Materials and Methods

This was a randomized, single-blind, parallel control study conducted from June 2014 to May 2015. Ethical clearance was obtained from institutional ethics committee before enrolling patients for the study. The sample size of 45 was decided based on the

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average number of patients with herpes zoster who attended the OPD of dermatology, AVBRH, Sawangi, Wardha in the past 3 years and follow-up period of 6 weeks. Patients were enrolled after considering various inclusion criteria such as patients of herpes zoster within 72 hours onset of rash, patients of both genders in the age group of 18–70 years, herpes zoster ophthalmicus without eye involvement, and exclusion criteria such as herpes zoster in pregnant and lactating mothers, patients of herpes zoster with diabetes mellitus, hypertension, tuberculosis, gastrointestinal ulcer disease, or with immune-compromised condition. A bowl containing total 45 chits with numbers written on it from A1–15, B1–15, and C1–15 was kept and all chits were shuffled properly after each patient's selection. Each patient was asked to select one chit and was enrolled according to the chosen group.

Written informed consent was obtained from each patient. A detailed history of age, sex, onset of the rash, and duration and severity of pain was taken. Pain severity was graded after allotment of patients in each of the three groups using verbal rating scale (VRS) [Figure 1]. It is easy to use the four-point verbal categorical rating scale (VRS). It categorizes pain as mild, moderate, and severe and is used as a screening instrument.[1] In our study, we had categorized herpes zoster pain in three grades as mild, moderate, and severe using VRS. Treatment given to each group included, Group A (control) –Tab.valacyclovir (1 g tds × 7 days), Group B–Tab.valacyclovir (1 g tds × 7 days) + Cap. pregabalin (75 mg bd × 1month) and Group C –Tab. valacyclovir (1g tds × 7 days) + Cap.pregabalin (75 mg bd × 1month) + Tab.methylprednisolone (0.64 mg/kg body weight in two divided doses for 7 days). Each patient was given medicines according to the allotted group enclosed in a white unmarked envelope. All the patients of the three groups were instructed to apply topical calamine lotion twice a day for 7 days followed by mupirocin cream twice a day for another 7 days.

Patients were followed at the end of 1 week (to assure compliance of medication), 4 weeks (to asses complete resolution of acute herpetic pain), and at 6 weeks (to note patients with still persisting pain, i.e., PHN). The recruitment, randomization and treatment process for the present study has been summarized in Flowchart 1.

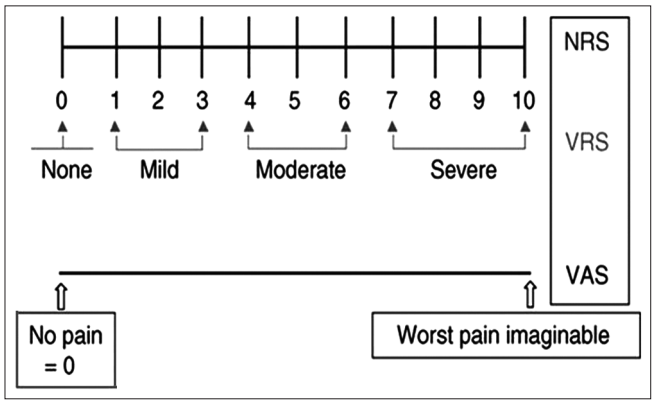

Figure 1: Verbal rating scale (VRS)

During this follow-up period, improvement in acute pain was assessed based on the presence or absence of pain using VRS. Patients with complete resolution of pain till the end of 4 weeks were considered completely cured. Patients were monitored for side-effects during the follow-up period.

Statistical analysis was done by using descriptive and differential statistics using Chi-square test. Software used in the analysis was SPSS 17.0 version and graphpad prism 5.0 version. $P < 0.05$ is considered as the level of significance.

Results

The distribution of demographic features related to age ($P = 0.19$) [Table 1], sex ($P = 0.52$), and intensity of pain ($P = 0.067$) [Table 2] were comparable in all the three groups. Majority of patients in all groups had either pricking and/or burning type of pain beginning 2–3 days before onset of rash. Out of the total 45 patients, in group A 1 had mild, 10 moderate, and 4 severe pain; in group B, 2 had mild, 10 moderate, and 3 severe pain; and in group C, 0 had mild, 12 moderate, and 3 severe pain before starting the treatment. At the end of 4 weeks in the group A, 4 patients had mild, 8 moderate, and 1 severe pain; in group B, 7 patients had mild, 4 moderate, and 0 severe pain; in group C, 6 patients had mild, 1 moderate, and 0 severe pain.

Complete resolution of acute pain at the end of 4 weeks after the onset of rash was seen in 2 patients (13.33%), 4 patients (26.67%), and 8 patients (53.33%) in groups A,

Table 1: Age-wise distribution of patients

Age Group (years)	Group A	Group B	Group C	χ^2
Up to 20	0 (0%)	1 (6.67%)	1 (6.67%)	13.63
21-30	5 (33.33%)	5 (33.33%)	6 (40%)	P=0.19,
31-40	4 (26.67%)	1 (6.67%)	4 (26.67%)	NS
41-50	4 (26.67%)	4 (26.67%)	0 (0%)	
51-60	1 (6.67%)	0 (0%)	3 (20%)	
>60	1 (6.67%)	4 (26.67%)	1 (6.67%)	
Total	15 (100%)	15 (100%)	15 (100%)	
Mean age	39	41.73	37.20	
SD	14.77	15.26	15.13	
Range	23-80	18-66	19-70	

Table 2: Intensity of pain in three groups at pretreatment stage

Intensity of pain	Group A	Group B	Group C	χ^2
Mild	1 (6.7%)	2 (13.3%)	0 (0%)	2.45
Moderate	10 (66.7%)	10 (66.7%)	12 (80%)	P=0.67,
Severe	4 (26.7%)	3 (20%)	3 (20%)	NS
Total	15 (100%)	15 (100%)	15 (100%)	

B, and C, respectively. Reduction in acute pain was statistically significant for all the groups; A (P = 0.0002), group B (P = 0.001), and C (P = 0.001) compared to the baseline value at the end of 4 weeks [Figure 2]. At the end of 6 weeks percentage-wise incidence of persistence of pain was more in Group A and B as compared to Group C, and it was statistically significant (P = 0.0001) [Figure 3]. PHN was observed in 13 patients (86.67%) of group A compared to 11 patients (73.33%) and 7 patients (46.67%) in group B and C, respectively [Figure 4]. No significant side-effects were observed in any group except vomiting in 1 patient of group A, somnolence in 1 patient, anddizziness in 2 patients of group B and group C each.

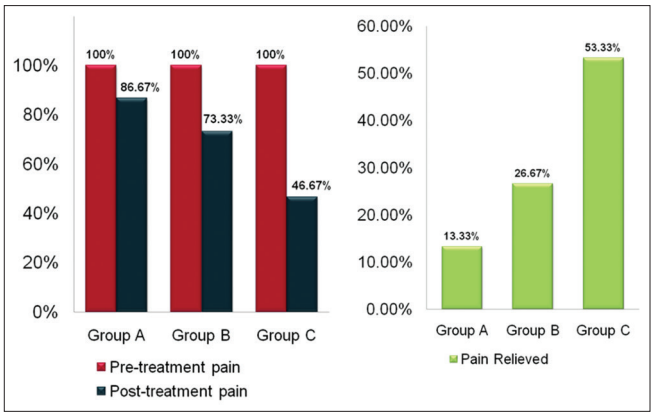

Figure 2: Complete resolution in acute pain was statistically significant, i.e., P = 0.0002 for group A and P = 0.0001 for groups B and C, respectively, individually compared to the baseline at the end of 4 weeks

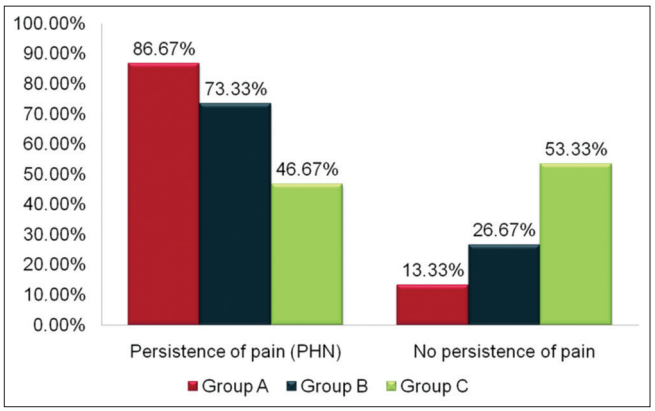

Figure 3: At the end of 6 weeks percentage wise incidence of persistence of pain was more in Group A and B as compared to Group C and it was statistically significant (P = 0.0001)

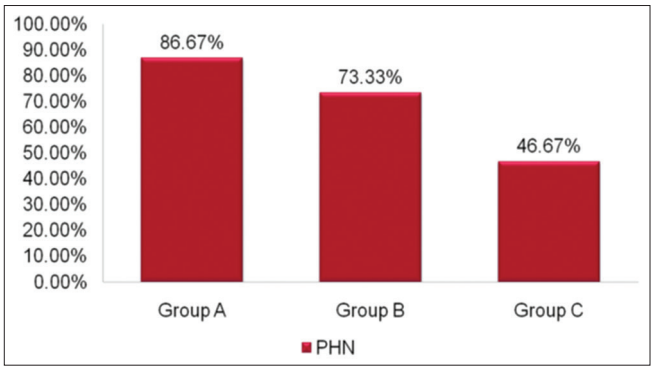

Figure 4: In group A, PHN was observed in 13 patients (86.67%) compared to 11 patients (73.33%) and 7 patients (46.67%) in group B and C, respectively

Discussion

Early institution of antiviral drug not only accelerates the healing of rash but also reduces the severity of acute pain, thus reducing the incidence of chronic pain. Among all the antiviral drugs (acyclovir, valacyclovir, andfamcyclovir), we have studied valacyclovir which is l-valyl ester of acyclovir with better bioavailability, less frequency of dosing, and better treatment compliance than acyclovir.[2] Both valacyclovir and famciclovir reduce the time to complete cessation of zoster-associated pain including PHN compared to acyclovir.[3] Valacyclovir is also less expensive as compared to famcylcovir.[2]

Role of steroid in herpes zoster is controversial, but in a randomized placebo-controlled trial of acyclovir with and without prednisolone for herpes zoster, it was observed that combined antiviral and prednisolone therapy improve acute rash and neuritis but had no significant effect in chronic pain.[4]

In one of the placebo-controlled study on the efficacy of pregabalin in acute herpetic neuralgia, pregabalin was seen to be more effective compared to placebo in relieving acute pain of herpes zoster.[5]

Combination therapy has better effect than monotherapy. Early institution of valacyclovir, i.e., within 72 hours of onset of herpes zoster rash, effectively inhibits viral replication, thus reducing the pathological impact on skin and nerves.

Systemic corticosteroid can be considered in combination with antiviral drugs because it has marked anti-inflammatory effect leading to resolution of acute inflammatory phase of the disease.

Pregabalin is a calcium channel-2δ ligand with analgesic, anxiolytic, and anticonvulsant properties that acts both centrally and peripherally relieving acute neuropathic pain.

In the present study, cure rate for acute herpetic neuralgia was more in group C compared to group B and A. This could be explained by the synergistic effect of all the three drugs [Figure 5]. We used a combination of drugs to treat pain in its acute phase to prevent PHN, and all drugs had different mechanism of action targeting viral replication (valacyclovir), inflammation (methylprednisolone), as well as central and peripheral pain (pregabalin).

As age advances, chances of PHN also increase. Given the theoretic risk of immunosuppression with corticosteroids, some investigators believe that these agents should be used only in patients aged more than 50 years because

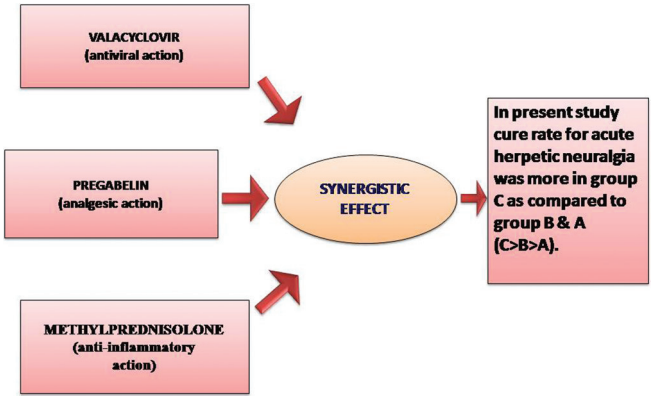

Figure 5: Synergistic effect due to rapid and effective viral inhibition due to early institution of valalcyclovir along with analgesic and anti-inflammatory effect of pregabalin and methylprednisolone, respectively

they are at a greater risk of developing PHN.[6] However, in our study, the average age of patients treated with this combination therapy was 39.31 years. Moreover, effective treatment duration was 1 week for valacyclovir and methylprednisolone whereas it was 1 month for pregabalin.

Common side-effects with valacyclovir are headache, nausea, and gastrointestinal disturbances;[7] side-effects with pregabalin include somnolence, dizziness, and headache,[8] and those associated with methylprednisolone areedema, hypertension, and nausea. Side-effects observed in this study were vomiting in 1 patient of group A, somnolence in 1 patient and dizziness in 2 patients of group B, and dizziness in 2 patients of group C.

There is a paucity of Indian studies regarding the efficacy of systemic corticosteroid and pregabalin in combination with antiviral drugs in the management of acute herpes zoster pain.

Conclusion

Combination therapy with valacyclovir, methylprednisolone, andpregabalin has better efficacy compared to valacyclovir and pregabalin and valacyclovir alone in the management of acute herpes zoster neuralgia. No significant side-effects were observed in any group except vomiting, somnolence, anddizziness. No treatment modality was 100% effective in the prevention of PHN. To our knowledge, till date, there are no reports regarding the efficacy of valacyclovir in combination with methylprednisolone and pregabalin in the management of acute herpes zoster pain.

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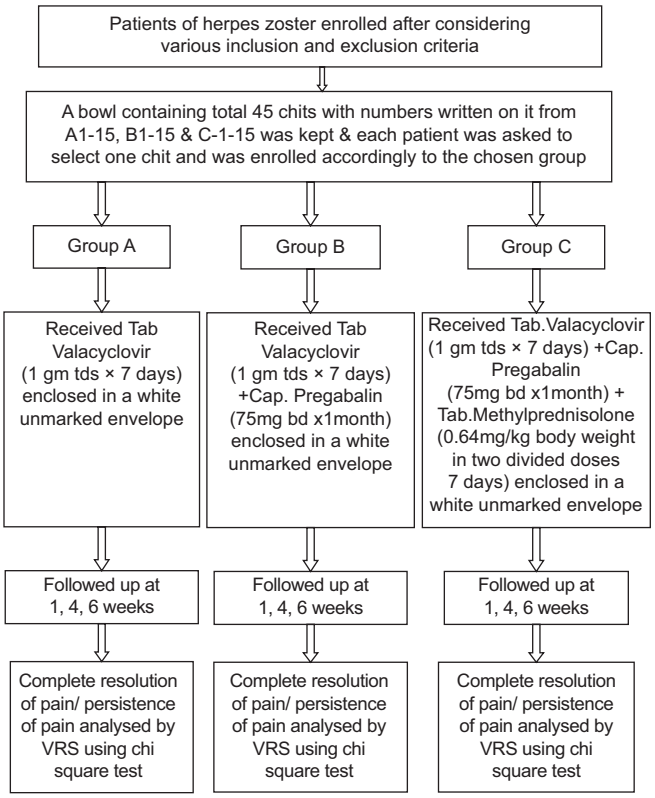
Nil.

Conflicts of interest

There are no conflicts of interest.



Flowchart 1: Consort flowchart

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