ORIGINAL ARTICLE

COMPARISON OF EFFICACY OF TWO DIFFERENT DOSES OF FAMCICLOVIR IN THE PREVENTION AND TREATMENT OF POSTHERPETIC NEURALGIA

Shawana Sharif, Faiza Aslam, Lubna Rani Faisal*, Muhammad Amer Saleem**

Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi Medical University, Rawalpindi, *Department of Dermatology, Islamic International Medical College, Riphah International University, Rawalpindi, **Benazir Bhutto Hospital, Rawalpindi Medical University, Rawalpindi-Pakistan

Background: Herpes Zoster is a common dermatological ailment. Various treatment modalities are in use for prevention of Post Herpetic Neuralgia (PHN) which is the most common complication of herpes zoster. Our study aimed to compare the efficacy of famciclovir 250 mg versus 500 mg in this regard. **Methods**: The study was conducted at a tertiary care hospital recruiting subjects by using simple random sampling, group A patients received famciclovir 250 mg thrice daily for 1 week while group B patients were administered 500 mg. Follow ups were arranged at 2, 4 & 12 weeks. Efficacy was assessed by pain evaluation as per numeric rating scale and counting number of skin lesions. PHN was taken as persistent pain at 4 weeks follow up. All the statistical analysis was done using SPSS. **Results:** A total of 30 patients were included in the study with each group (A & B) containing 15 patients each. Both dosing groups were statistically consistent with each other in reducing pain at 2, 4 and 12 weeks follow up. Skin lesions were not observed after 2 weeks in either group. The median of difference of pain scores at 2 weeks was similar as at 4 weeks. **Conclusion:** Famciclovir 250 mg thrice daily for one week is equally effective as 500 mg in treating active herpes zoster and prevention of PHN. However, long term follow-up is required for assessing the true incidence of PHN.

Keywords: Herpes Zoster; Famciclovir; Efficacy; Neuralgia; Postherpetic

Citation: Sharif S, Aslam F, Faisal LR, Saleem MA. Comparison of efficacy of two different doses of famciclovir in the prevention and treatment of postherpetic neuralgia. J Ayub Med Coll Abbottabad 2019;31(4 Suppl 1):668–71.

INTRODUCTION

Herpes Zoster (Shingles) is a common viral disease seen in dermatology clinics, affecting about 20% of the general population.[1] It usually manifests as a result of reactivation of endogenous varicella zoster virus that had persisted in latent form within sensory ganglia after an earlier attack of chickenpox.[2] Herpes Zoster is defined as new unilateral pain accompanied by dermatomal rash (papules & vesicles) with no alternate diagnosis.[3] It can have a variable presentation, however, in immune-competent host it usually subsides in 4 weeks or so after the initial onset of rash.[4]

The condition is associated with a number of complications that can even lead to mortality but the most common complication is post herpetic neuralgia (PHN) that results in a significant morbidity.[5,6] The pain is a prodromal symptom of herpes zoster that can be severe in the affected dermatome even before the appearance of rash but it typically settles with rash. In some patients it can persist for even years especially if elderly.[7] There is no consensus on the exact definition of PHN, however, PHN is mostly defined as the pain lasting for 4 weeks or beyond after the onset of rash.[8]

A number of modalities are in practice to control postherpetic neuralgia but none have proved superior without the use of antiviral agents.[9] Acyclovir is a common drug used for treating herpes zoster, however, famciclovir is superior to acyclovir in treating herpes zoster and preventing development of PHN. It also reduces the severity and duration of the PHN once it has established. It has a higher bioavailability and longer intracellular half-life in the virus infected cells as compared to acyclovir and continues to have anti-viral activity at serum levels even lower than inhibitory concentrations.[10] Therefore it can be used at lower doses and less frequently as compared to acyclovir without compromising the efficacy. The doses of famciclovir for uncomplicated herpes zoster is 250 mg thrice daily, 500 mg thrice daily or 750 mg once daily for 1 week.[11] However, it is expensive when given as 500 mg as compared to 250 mg regimen. At present, there is no consensus in literature on its dose and both 250 mg and 500 mg regimes are recommended. After an exhaustive search of various databases, we could not find any study comparing these two doses. Thus, the aim of this study was to establish whether the 250 mg dosage can emerge as a cost-effective treatment for prevention of PHN.

MATERIAL AND METHODS

A randomized controlled trial was conducted at the outpatient dermatology department of Benazir Bhutto Hospital, Rawalpindi for 1 year, starting from January 2018 till December 2018. After approval from the ethical committee, informed consent was obtained from

the patients fulfilling the criteria and wishing to participate in the study. Patients with uncomplicated herpes zoster, characterized by localized, cutaneous lesions (papules or vesicles) in the dermatomal distribution along with pain were included in the study by simple random sampling. All the patients were examined individually by two dermatologists to confirm the diagnosis. Only immune-competent patients over the age of 12 years with suspected herpes zoster were included in the study. In difficult cases, a Tzanc smear was done to confirm the diagnosis.

Patients with complications of herpes zoster (ocular involvement, severe disseminated infection, motor neuropathies, encephalitis or cerebrovascular complications), deranged renal function tests, diabetes or any other co-morbidity, pregnant or nursing women and patients receiving concurrent chemotherapy or immunosuppressive therapy as well as HIV sero-positive patients were excluded. The patients were divided into two groups randomly using random number table. Group A was given famciclovir in a dose of 250 mg thrice daily for 1 week and group B received famciclovir in a dose of 500 mg thrice daily for 1 week. All the patients were given Tab Diclofenac Sodium 50 mg twice daily along with topical application of Polymyxin B + Bacitracin (Polyfax) ointment thrice daily for 1 week as well.

Patients were asked specifically not to use any other drug with it and follow up at 2 weeks. At 2 weeks, clinical examination was repeated and the compliance of the patient was ensured by reviewing his trial diary entries. The clinical improvement of pain was assessed with numeric rating scale (NRS)-11 in which 0 indicated no pain and 10 was associated with worst pain possible along with dermatological manifestation by counting number of vesicles, papules and crusts. Subsequent visits were arranged at 4 and 12 weeks and all the above parameters were assessed again. The primary outcome was the efficacy of famciclovir in reducing PHN, PHN was taken as any score above 0 as per NRS-11 at 4 weeks follow up. All the statistical analysis was done using SPSS version 23.

RESULTS

A total of 30 patients were included in the study with each group (A and B) containing 15 patients each (1:1). Both study groups were homogenous based on the baseline characteristics of age, gender, duration of illness at time of presentation, mean scores of pains on NRS-11 before treatment & mean number of papules, vesicles and clustered lesions in the lesion before treatment. This is summarized in table-I.

Prior to initiation of treatment all the patients in each study group (n=30, 100%) had pain. At completion of 2 weeks, in 23 (76.7%) patients pain still persisted. Patients with persistent pain at the end of week 2 were 10 (66.7%) in group A while 13 (86.7%) in group B. The relative risk of persistence of pain in Group A subjects as compared to group B at completion of 2 weeks was 0.76 (95% CI, 0.51–1.15) with a p=0.20. At completion of 4 weeks the proportion of such patients declined with only 6 (20%) patients overall who complained of any pain. Five (33.3%) belonged to group A and only 1 (6.7%) patient belonged to group B with a relative risk of 6.00 (95% CI, 0.81–43.99) and p=0.07. On follow up at 12 weeks, the comparison of PHN showed that pain persisted in only 3 (10%) of the total number of patients, amongst whom 2 (13.3%) patients belonged to group A and 1 (6.7%) belonged to group-B, but this difference was not statistically significant with relative risk of 2.00 (95% CI, 0.20–19.77) and p=0.55. This is depicted in figure-I.

The comparison of the mean pain scores at end of 2 weeks (3.07±2.74 in group A vs 1.55±2.80 in group B, p=0.68) and 4 weeks (1.13±2.13 in group A versus 0.20±0.07 in group B, p=0.23) showed a statistically non-significant difference. This is displayed in figure-2. There were highly statistically significant differences when pain scores at the three points of time were compared with each other within both the groups except that the median of differences of scores of pain at 4 weeks were similar as scores of pain at completion of 12 weeks. The same was true for the comparison of number of skin lesions. This is summed up in table-2. Skin lesions (papules, vesicles and crusted lesions) were observed in all 30 (100%) patients before treatment. Only one patient in group A had persistent dermatological manifestation at the end of 2 weeks. Afterwards no papules, vesicles or crusted lesions were observed in any patient at all.

As regards the comparison of adverse effects reported within 12 weeks by patients in both the study groups, there was no statistically significant difference observed in the proportions. The comparison of side effects is mentioned in the table-3.

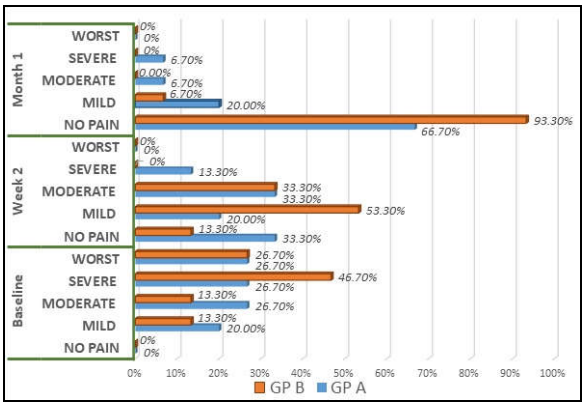

Figure-1: Comparison of severity of pain in study Group A and Group B reported at two follow up visits.

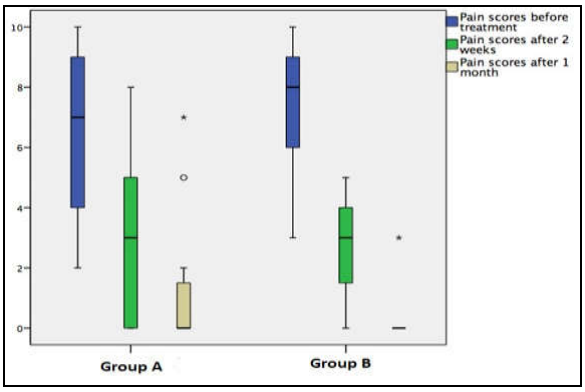

Figure-2: Mean scores of pain in patients of group a and group b at 2 weeks and 4 weeks (1 month).

Table-1: Demographics & baseline characteristics of the subjects

Demographics & baseline characteristics (n=30)		Group A (n=15)	Group B (n=15)	*p*-values
Gender	Male n (%)	8 (50%)	8 (50%)	1.0
	Female n (%)	7 (50%)	7 (50%)	
Age (Mean±SD)		39.80±12.26	46.80±10.69	0.10
Duration of Illness in Days (Mean±SD)		3.53±1.55	3.73±1.58	0.87
Pain on NRS Before Treatment (Mean±SD)		6.40±2.87	7.27±2.37	0.43
Number of Papules, Vesicles and Crusted Lesions Before Treatment (Mean±SD)		125.33±140.56	83.33±44.94	0.87

NRS=Numerical rating scale for pain (0–10)

Table-2: Comparison of pain scores at different points of time within Group A and Group B

Scores of Pain	Group A *p*-values	Group B *p*-values	Skin Lesions	Group A *p*-values	Group B *p*-values
Baseline vs at 2 weeks	∗0.001	∗0.001	Baseline vs at 2 weeks	∗0.001	∗0.008
Baseline vs at 4 weeks	∗0.001	∗0.001	Baseline vs at 4 weeks	∗0.001	∗0.001
Baseline vs at 3 months	∗0.001	∗0.001	Baseline vs at 3 months	∗0.001	∗0.001
At 2 weeks vs at 4 weeks	∗0.007	∗0.001	At 2 weeks vs at 4 weeks	∗0.018	∗∗0.001
At 2 weeks vs at 3 months	∗0.005	∗0.001	At 2 weeks vs at 3 months	∗0.017	∗0.001
At 4 weeks vs at 3 months	0.112	0.317	At 4 weeks vs at 3 months	1.000	1.000

∗Highly Statistically significant difference

Table-3: Comparison of adverse effects reported within 12 weeks by patients in both the study groups

Adverse Effects	Group A n=15		Group B n=15		*p*-values
	n	%	n	%	
Headache	3	20	4	26.66	0.67
Nausea	2	13.33	2	13.33	1.00
Vomiting	3	20	2	13.33	0.62
Abdominal pain	2	13.33	3	20	0.62
Diarrhea	2	13.33	1	6.66	0.54
Flatulance	2	13.33	2	13.33	1.00
Pruritis	0	0	1	6.66	0.31
Rashes	0	0	0	0	1.0

DISCUSSION

Herpes Zoster and it's most common and debilitating complication, i.e., PHN has implicated some serious therapeutic challenges to the physicians. Introduction of antiviral drugs in treating herpes zoster has revolutionized its management. It leads to rapid improvement of pain and dermatological manifestation of disease and is also able to prevent PHN and reduce the duration and severity of PHN once it has occurred.[12]

Famciclovir is as effective as acyclovir but it is expensive when given as 500 mg thrice daily for 1 week as compared to 250 mg dose. It has the advantage of convenient dosing and increases the compliance of patient.[13] Pakistan is a developing country with a high number of people with low socio-economic status. One of the major hindrances in treating patients presenting to the government hospitals of the Pakistan is the cost of treatment. It is a major challenge for the physicians to advise an effective treatment that should be cost-effective too.

Acute phase of herpes zoster is quite painful and cosmetically unappealing due to papules and vesicles. Famciclovir at a dosage of 250 mg has similar proven efficacy as acyclovir in a number of trials in treatment of herpes zoster.[14,15] Another multinational and multicenter study conducted in 2004 showed similar effects of famciclovir 250 mg thrice daily and 500 mg twice daily in treating acute pain of herpes zoster but effect on post herpetic neuralgia was not assessed.[16] Both tested doses of famciclovir in our study showed similar efficacy in treating active phase of herpes zoster as well as preventing PHN.

The follow up of patients was done at 2, 4 and 12 weeks. The proportion of pain free patients in

both groups had no statistical difference at all of these points of follow up. The mean of pain scores between groups A & B at 2 weeks was similar as at 4 weeks which was taken as the threshold time for defining PHN in our study. The skin lesions were also not seen on follow up after 2 weeks in both groups. Pain persisted in only 3 patients (Group A=2, Group B=1) at 12 weeks follow up and these patients should have been followed up further in the future to denote the true incidence of postherpetic neuralgia. Regarding the safety profile of the two doses, there was no difference observed in the adverse effects experience by patients in the two groups at various points of follow up.

CONCLUSION

Famciclovir at a dose of 250 mg thrice daily for one week is as effective as 500 mg thrice daily for one week in treating pain of active herpes zoster as well as preventing PHN. Similar effects are also seen on reduction of skin lesions. So, low dose famciclovir can emerge as a cost-effective antiviral with easy dosing schedule in prevention of PHN. Further studies with larger sample sizes and longer follow up periods are needed to confirm the effect of low dose famciclovir in preventing PHN.

AUTHORS' CONTRIBUTION

SS: conceptualization, data collection, manuscript writing. FA: data collection, data analysis. LRS: data collection, data analysis. MAS: manuscript writing, proof reading.

REFERENCES

1. Gialloreti LE, Merito M, Pezzotti P, Naldi L, Gatti A, Beillat M, *et al*. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis 2010;10(1):230.
2. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Neurological disease produced by varicella zoster virus reactivation without rash. Curr Top Microbiol Immunol 2010;342:243–53.
3. Bulilete O, Leiva A, Rullán M, Roca A, Llobera J, PHN Group. Efficacy of gabapentin for the prevention of postherpetic neuralgia in patients with acute herpes zoster: A double blind, randomized controlled trial. PloS One 2019;14(6):e0217335.
4. Engler D, Sibanda M, Motubatse HJ. Shingles. S Afr Pharm J 2017;84(6):60–4.
5. Mahamud A, Marin M, Nickell SP, Shoemaker T, Zhang JX, Bialek SR. Herpes Zoster-Related Deaths in the United States: Validity of death certificates and mortality rates, 1979-2007. Clin Infect Dis 2012;55(7):960–6.
6. Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. BMC Med 2010;8(1):37.
7. Fashner J, Bell AL. Herpes zoster and postherpetic neuralgia: prevention and management. Virus 2011;83(12):1432–7.
8. Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect 2009;137(1):38–47.
9. Schmidt SAJ, Rowbotham MC. Aggressive Noninvasive Treatment of Acute Herpes Zoster for the Prevention of Postherpetic Neuralgia. In: Herpes Zoster: Postherpetic Neuralgia and Other Complications: Springer, 2017; p.341–64.
10. Stoopler ET, Balasubramanlam R. Topical and systemic therapies for oral and perioral herpes simplex virus infections. J Calif Dent Assoc 2013;41(4):259–62.
11. McDonald EM, de Kock J, Ram FS. Antivirals for management of herpes zoster including ophthalmicus: a systematic review of high-quality randomized controlled trials. Antivir Ther 2012;17(2):255–64.
12. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clin Proc 2009;84(3):274–80.
13. Gopal MG, Shannoma SK, Ramesh M, Nandini AS, Manjunath NC. A comparative study to evaluate the efficacy and safety of acyclovir and famciclovir in the management of herpes zoster. J Clin Diagn Res 2013;7(12):2904–7.
14. Gross G, Schöfer H, Wassilew S, Friese KE, Timm A, Guthoff R, *et al*. Herpes zoster guideline of the German Dermatology Society (DDG). J Clin Virol 2003;26(3):277–89.
15. Wassilew SW. Brivudin compared with famciclovir in the treatment of herpes zoster: effects in acute disease and chronic pain in immunocompetent patients. A randomized, double-blind, multinational study. J Eur Acad Dermatol Venereol 2005;19(1):47–55.
16. Shafran SD, Tyring SK, Ashton R, Decroix J, Forszpaniak C, Wade A, *et al*. Once, twice, or three times daily famciclovir compared with aciclovir for the oral treatment of herpes zoster in immunocompetent adults: a randomized, multicenter, double-blind clinical trial. J Clin Virol 2004;29(4):248–53.

Submitted: 8 July, 2019	*Revised:20 October, 2019*	*Accepted: 28 October, 2019*

Address for Correspondence:

Shawana Sharif, Department of Dermatology, Benazir Bhutto Hospital, Rawalpindi Medical University, Rawalpindi-Pakistan

Email: shawana.sharif@gmail.com