

A COMPARATIVE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF VALACYCLOVIR AND FAMCYCLOVIR IN THE MANAGEMENT OF HERPES ZOSTER IN A TERTIARY CARE HOSPITAL IN PUDUCHERRYR. Indradevi¹, K. Manoharan², P. Oudeacoumar³, S. Karthikraja⁴, N. Azeem Jaffar⁵**HOW TO CITE THIS ARTICLE:**

R. Indradevi, K. Manoharan, P. Oudeacoumar, S. Karthikraja, N. Azeem Jaffar. "A Comparative Study to Evaluate the Efficacy and Safety of Valacyclovir and Famcyclovir in the Management of Herpes Zoster in a Tertiary Care Hospital in Puducherry". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 21, May 26; Page: 5804-5812, DOI: 10.14260/jemds/2014/2666

ABSTRACT: OBJECTIVE: The objective of this study was to compare the efficacy and safety of Valacyclovir and Famcyclovir in the management of Acute Herpes Zoster. **MATERIALS AND METHODS:** Relevant data were taken from 162 patients with herpes zoster who presented within 72 hours of onset of rash and were randomized into 2 groups of 81 each. The 1st group received Valacyclovir 1gm thrice a day for 7 days while those in the 2nd group received Famcyclovir 500 mg thrice a day for 7 days respectively and evaluated at the end of each week upto 6 weeks period and examined for full crusting of lesions, complete healing of the lesion and loss of acute pain (visual analogue scale scores for pain). Safety assessment was based on adverse effects. **RESULTS:** The intent to treat analysis (162 Pts) showed that valacyclovir for 7 days significantly accelerated the resolution of pain in Herpes zoster pts ($P=0.00014$) compared with famcyclovir; median pain duration were 21 and 22 days respectively. There was no difference between treatments in time taken for healing of lesions. Adverse effects like nausea, vomiting, diarrhoea and headache were commonly reported in both groups. Valacyclovir was found to be statistically superior over Famcyclovir in terms of G.I adverse effects. Compliance was also better with Valacyclovir. **CONCLUSION:** Oral Valacyclovir administered three times daily for 7 days during acute zoster infection offers significant benefit by providing a well-tolerated, cost effective and accelerated rate of resolution of pain and maintains the favorable safety profile compared to oral Famcyclovir.

KEYWORDS: Valacyclovir, Famcyclovir, Herpes zoster.

INTRODUCTION: Herpes zoster, also known as shingles, results due to reactivation of an earlier latent infection with the varicella zoster virus (VZV) in dorsal root ganglia, whereas varicella is generally a disease of childhood, herpes zoster and post-herpetic neuralgia become more common with increasing age.¹ Factors that decrease immune function, such as human immunodeficiency virus infection, chemotherapy, malignancies and chronic corticosteroid use, may also increase the risk of developing herpes zoster.^{1,2}

Reactivation of latent varicella-zoster virus from dorsal root ganglia is responsible for the classic dermatomal rash and pain that occur with herpes zoster. Burning pain typically precedes the rash by several days and can persist for several months after the rash resolves. With postherpetic neuralgia, a complication of herpes zoster, pain may persist well after resolution of the rash and can be highly debilitating.² Herpes zoster is usually treated with orally administered acyclovir. Other antiviral medications include famciclovir and valacyclovir.

The antiviral medications are most effective when started within 72 hours after the onset of the rash. Famcyclovir, a new antiviral agent was approved for marketing by FDA in June 1994 for the

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management of acute Herpes Zoster. It is well absorbed (77% bioavailable oral form of Penciclovir) with activity against varicella zoster virus.

It selectively gets activated in virus infected cells through phosphorylation to antiviral compound Famcyclovir triphosphate. Valacyclovir, the L-valyl ester of Acyclovir was developed to increase oral bioavailability of Acyclovir by 70%. Valacyclovir is better absorbed than Acyclovir due to an active stereo selective transporter in intestinal brush border membrane.^{3,4}

MATERIAL AND METHODS: A prospective study was conducted on patients with herpes zoster attending Department of Dermatology at Aarupadai Veedu Medical College and Hospital, Pondicherry, India, during the period of December 2010 to January 2013.

Data Collection: A proforma containing detailed information on each patient was prepared according to the protocol designed for patients with reference to their age, sex, prodromal symptoms, past history of chickenpox, family history, history of diabetes, systemic steroid therapy, radiotherapy and previous malignancy. Informed consent was taken from all the patients. A detailed general physical and systemic examination was carried out to find any signs of major illness. Routine investigations of blood and urine were done in all patients.

Diagnosis was confirmed by Tzanck smear. Smears were prepared from the floor of the fresh vesicle and were stained with Leishman stain to detect multinucleated giant cells. Biopsy was done in few patients to study the histopathology changes. Ethical clearance was obtained from the institutional ethics committee.

Selection Criteria for Patients: A total of 162 patients with herpes zoster were enrolled in the study. Herpes zoster was diagnosed clinically based on the presence of tense, grouped, vesiculobullous lesions on an erythematous base, unilaterally in a dermatomal distribution.

Inclusion Criteria: Immunocompetent patients over the age of 40 years with uncomplicated herpes zoster, characterized by localized, cutaneous lesions (papules or vesicles) presenting within 72 hours of the onset of the rash.

Exclusion Criteria:

The exclusion criteria for the patients were:

1. Pregnant and nursing women.
2. Patients treated with other antiviral medications and Immunomodulator agents.
3. Known immunocompromised status.
4. Patients with pre-existing renal and hepatic impairment.

Efficacy Assessment: Patients were evaluated for pain and healing of the cutaneous lesions on day 7 after initiation of therapy and every week thereafter, for a period of six weeks. The primary variables evaluated at each visit were: the time taken for the full crusting of the lesions, lesions were defined to be fully crusted when all the papules and vesicles in the affected dermatome had resolved and crusts had appeared, the time taken for complete healing of the lesion, healing was defined as the first time

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in which a patient had no papules, vesicles or crusts and after which did not develop them at any later visit.

Time taken for loss of acute pain was assessed by visual analogue scale; the visual analogue score 8 was calculated as follows:

No pain:	score 0
Mild pain:	score 1, 2, 3
Moderate pain:	score 4, 5, 6
Severe pain:	score 7, 8, 9
Worst ever felt pain:	score 10

The secondary parameters included: assessing the primary variables in the patients aged above 60 years with each drug and the relative efficacy of each drug in different dermatomes (cranial, cervical, thoracic, and lumbar) in patients aged above 60 years.

Safety Assessments: The number and percentage of patients reporting at least one adverse event during the treatment protocol were assessed. Drug related adverse events were defined as those adverse events that were related or possibly related to the study therapy or as being of unknown causality. The frequently reported events were nausea, headache, vomiting and constipation. The complete blood cell count, urine analysis and serum biochemistry test at baseline and at the end of treatment were mentioned.

Ethics: Cost of investigation (if any) will be borne completely by investigator. The personal details of the subject will be kept confidential.

STATISTICS: Continuous variables were described by mean, median, standard deviation and range. Categorical data were summarized by counts and percentages.

The statistical methods were done through IBM SPSS for Windows (version 19.0). P value calculated using unpaired "t" test.

RESULTS: In total, 162 patients were enrolled in the study and randomized into Valacyclovir and Famciclovir groups in 1:1 ratio. The overall mean age in group Valacyclovir was 53.64 years and group Famciclovir was 51.38 years, suggesting that both the groups were comparable in respect to their ages as seen in [Table 1].

Majority of patients (50%) on an average from both groups, were in the age-group of 50- 59 years and only few percentage were in the age-group of above 70 years as seen in [Table 2/Fig. 1].

The male: female ratio in Valacyclovir group and Famciclovir group was 1:0.84 and 1:0.88 respectively, with slightly more number of males in both the groups as shown in [Table 3].

Thoracic dermatomes were most commonly involved dermatomal segments in both the groups [Table 4/Fig. 2].

For the majority of patients in both the groups, the duration of rash at the start of treatment was between 48 and 72 hours.

None of the patients in either group had bilateral involvement of the primary affected region.

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The primary variables considered were, time taken for full crusting of the lesion, complete healing and loss of acute pain. Lesions were defined to be fully crusted, when all the papules and vesicles in the affected dermatome had resolved and crusts had appeared. Lesions were defined completely healed, when all the crusts had fallen off with absence of papules and vesicles.

All patients in both treatment groups experienced pain at the time of screening and the distribution of pain intensity was comparable in the two groups. Most patients had moderate pain at the time of screening. Pain was described in decreasing order of frequency as pricking, burning, stabbing, shooting and throbbing in both the groups.

The mean number of days taken for full crusting, complete healing of lesions and acute loss of pain in valacyclovir group was 9.73 days, 20.32 days and 21.03 days respectively; in Famcyclovir group was 10.43 days, 20.66 days and 22.15 days and p-values were calculated as seen in [Table 5/ Fig. 3]. Thus, the time taken for complete healing is insignificant but the time taken for loss of acute pain is significant.

The time taken for full crusting in both the groups in patients above 60 years of age was 13.75 days in Valacyclovir and 12.8 days in Famcyclovir. Time taken for complete healing was 22.5 days in Valacyclovir and 22.6 days in Famcyclovir, for acute loss of pain was 23.5 days in Valacyclovir and 24.6 days in Famcyclovir group. And its p-value is seen in [Table 6].

No clinically significant difference was found in the results of urinalysis, hematology and serum biochemistry at baseline between the treatment groups.

The most common adverse effects reported in both the groups were nausea, vomiting, diarrhoea, dizziness and headache. 82% of valacyclovir patients had no adverse effects, and the drug was well-tolerated except for 4 patients who had headache and 5 patients who complained of nausea.

Adverse effects were slightly higher in Famcyclovir, 10 patients having nausea and vomiting, 7 patients having headache and 4 patients having dizziness and diarrhoea.

Drug	Mean Age	SD	Minimum	Maximum
V	53.64	8.77	40	78
F	51.38	7.73	40	79

Table 1: Mean age and SD in both the groups

Age - group	Valacyclovir		Famcyclovir	
	No.	%	No.	%
40-49	25	30.86	35	43.21
50-59	45	55.55	39	48.14
60-69	6	7.40	5	6.17
70-79	5	6.17	2	2.46
Total	81	99.98	81	99.98
Mean ± SD	53.64 ± 8.77		51.38 ± 7.73	

Table 2: Age distribution in both the groups

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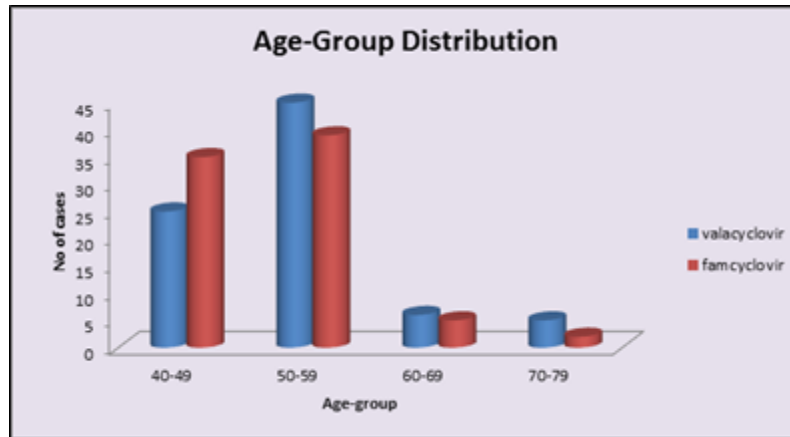


Figure 1

Gender	Valacyclovir		Famcyclovir	
	No.	%	No.	%
Male	44	54.32	42	51.85
Female	37	45.67	39	48.14
Total	81	100	81	100

Table 3: Gender distribution in both the groups

Distribution	Valacyclovir	Famcyclovir
Thoracic	33 (40%)	30(37%)
Cervical	16(20%)	19(23%)
Trigeminal	20(25%)	19(23%)
Lumbar	12(15%)	13(17%)

Table 4: Dermatomal distribution in both the groups

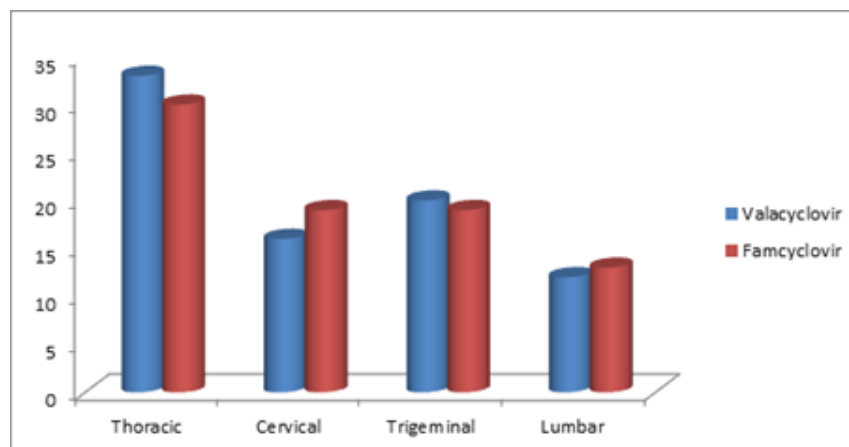


Figure 2: Dermatomal distribution

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Variables	Full Crusting		Healing		Loss of Pain	
	V	F	V	F	V	F
Mean	9.73	10.43	20.32	20.66	21.03	22.15
Sd	1.85	1.71	1.61	1.87	1.84	1.97
P<	0.00216		0.1933		0.00014	

Table 5

Mean time taken for full crusting, healing and loss of acute pain in both the groups

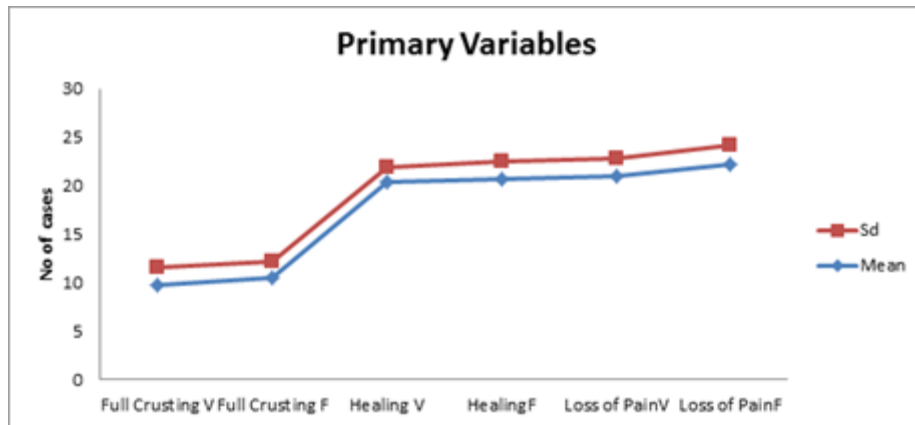


Figure 3

Variables	Full Crusting		Healing		Loss of Pain	
	V	F	V	F	V	F
Mean	13.75	12.8	22.5	22.6	23.5	24.6
Sd	0.46291	0.83666	1.414214	0.83666	0.46291	1.516575

Table 6

Mean time taken for full crusting, healing and loss of acute pain in both the groups in patients >60yrs.

DISCUSSION: Acute Herpes Zoster is a painful debilitating condition. It occurs due to reactivation of varicella zoster virus from a latent infection of dorsal sensory or cranial nerve ganglia.¹ Declining cell mediated immunity as a result of aging, immunosuppressive illnesses and immunosuppressive agents increase the risk of herpes zoster. The pain of herpes zoster is the principle reason most patients seek medical attention. Persistence of pain after rash healing may occur more commonly in the elderly and result in post herpetic neuralgia which is difficult and often costly to treat effectively.²

Antiviral therapy has been shown to decrease the duration of herpes zoster and severity of pain associated with rash. An increased acute pain and rash severity are risk factors for PHN. Hence the use of antiviral therapy may have a favorable effect on acute pain and post herpetic neuralgia.

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The oral nucleoside analogue, acyclovir is widely used in the treatment of herpes zoster. Famcyclovir and Valacyclovir are the two other FDA approved drugs in the management of acute herpes zoster. Famcyclovir was approved by FDA in June 29, 1994.³ Valacyclovir was approved by FDA in December 15, 1995.⁴ In the present study, we have compared the efficacy of Valacyclovir 1g thrice daily with Famcyclovir 500mg thrice daily given for a period of 7 days in a treatment of acute herpes zoster. Both are new antiviral prodrug.

Valacyclovir is a prodrug and metabolised to acyclovir, the oral bioavailability of acyclovir from Valacyclovir is 54% as compared to 15- 30% for acyclovir.⁵

Famcyclovir is a prodrug for the metabolite Penciclovir, the mean oral bioavailability from Famcyclovir is 77%. They both reduce viral replication by inhibiting viral DNA polymerase.⁶

If given within 72 hours of first HZ lesion, both provide modest decrease in time taken for full crusting, time taken for healing and loss of acute pain. The present study was aimed to assess the efficacy and safety of acyclovir and famcyclovir in the treatment of acute herpes zoster.⁷ At the end of each week the patients were evaluated for the primary endpoints, time taken for full crusting of the lesions, complete healing of the lesion and loss of acute pain.

The secondary parameters included: assessing the primary variables in the patients aged above 60 years with each drug, and the relative efficacy of each drug in different dermatomes (cranial, cervical, thoracic, lumbar) in patients aged above 60 years were also considered [Table/ Fig- 7, 8, 9]. The median time taken for full crusting of the lesions in both the groups was 10 days, According to Shafran et al⁸ the median time for full crusting was 10 days in both the groups. Our findings are in agreement with Shafran et al.⁸ The median time taken for complete healing of the lesions in both the groups was 20days.

The time taken for complete healing of the lesions in the patients above 60 years, belonging to Valacyclovir group was considerably faster than the Famcyclovir group. The median time taken for loss of acute pain in both the groups was 21 days. A significant decrease in mean VAS scores when compared to the previous scores was observed within the treatment groups for both the drugs.

Both the treatments were effective in reducing zoster associated abnormal sensations. Since post-herpetic neuralgia increases with increasing age, we studied the effect of these drugs in patients above 60years of age-group, with respect to the dermatome affected, full crusting, complete healing and loss of acute pain. It was observed that the patients above 60 years of age took considerably longer period for complete healing of the lesion and loss of acute pain i.e., 24 days.

However, the time taken for full crusting of the lesion remained same as the lesser age-groups. There was no significant difference between the effects of drugs in different dermatomes in these patients. There were no clinically significant differences in the nature, frequency, or severity of adverse events between the two treatment groups.

No serious adverse events were observed in either group to warrant withdrawal from the study. The adverse effects noted were nausea, vomiting, dizziness, diarrhoea and abdominal pain. 5% of our study patients had PHN, 2 of Valacyclovir group and 3 belonging to Famcyclovir group. All the 5 patients were in the age group 60-80 years, 3 patients were above 70 years and 2 were in 60-70 years of age-group.

Since our study did not include a placebo control; no conclusion can be drawn regarding the effect of both the drugs on PHN. Hence, we could not compare our observation regarding the efficacy of each drug in reducing the duration of PHN.^{8,9}

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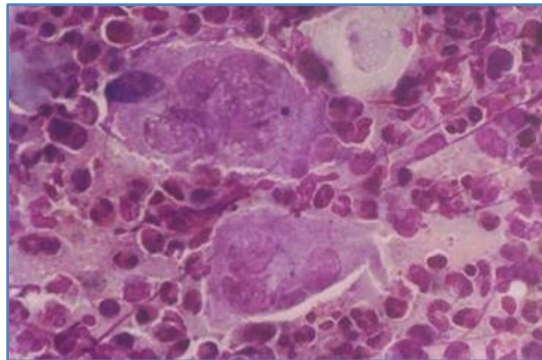
CONCLUSION: Thus in the present study, both Famcyclovir and Valacyclovir have a modest beneficial effect in the treatment of acute herpes zoster if given within 72 hours of onset of rash. Valacyclovir offers significant benefit by providing well tolerated cost effective convenient dosage regime and accelerated rate of resolution of pain compared to Famcyclovir. It also maintains favorable safety profile compared to Famcyclovir.

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TZANCK SMEAR STAINED WITH LEISHMAN'S STAIN SHOWING MULTINUCLEATED GAIANT EPITHELIAL CELLS



Pretreatment for Valacyclovir



Post treatment for Valacyclovir

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