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Original Article

Efficacy and Safety of Valacyclovir over Acyclovir-A Study of 50 Herpes Zoster Patients in FMCH, Faridpur

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Abstract:

Acyclovir has well-documented efficacy and tolerability in the treatment of herpes zoster. Its limited oral bioavailability and short half-life, however, necessitates frequent dosing. Valacyclovir, the l-valyl ester of acyclovir, could be rapidly converted to acyclovir after oral administration, resulting in a three to five fold increase in acyclovir bioavailability compared with oral acyclovir in humans. The study was done in the department of Dermatology and Venereology, Faridpur Medical College Hospital (FMCH), Faridpur, Bangladesh from July 2015 to December 2016 to compare the safety and efficacy of valacyclovir with acyclovir in the treatment of herpes zoster. Relevant data was taken from 50 patients presenting with herpes zoster within 72 hours after the onset of rash and were randomized into two groups of 25 each to receive one of the following treatments: valacyclovir 1000 mg three times daily for 7 days or acyclovir 800 mg five times daily for 7 days for each group. Patients were followed up on day 7, 14, 22 and 29 to assess the rate of resolution of pain, cessation of abnormal sensations, rate of rash healing, new lesion formation and occurrence of complications or adverse effects. The intent-to-treat analysis showed that valacyclovir significantly accelerated the resolution of zoster-associated pain compared with acyclovir; on day 29, the valacyclovir group was 44% superior to the acyclovir group. The rate of cessation of abnormal sensations, rash healing and complications or adverse effects was similar with both the treatments. There were no clinically significant differences in the nature, frequency or severity of adverse events between the two treatment groups. Thus, we conclude that in the management of herpes zoster, valacyclovir accelerates the resolution of pain and offers a simpler dosing, and maintains the favorable safety profile of acyclovir.

Key words: Acyclovir, Valacyclovir, Herpes Zoster.

Introduction:

Herpes zoster, also known as shingles, is caused by re-activation of VZV (Varicella Zoster Virus). Following primary infection or vaccination, VZV remains latent in the sensory dorsal ganglion cells. The virus begins to replicate at some latent time, traveling down the sensory nerve into the skin[1-3]. As re-activation of the virus is linked to diminished virus specific immunity, it develops mainly in the elderly and immunocompromised patients[4]. Acute herpes zoster patients with rashes distributed over one or more dermatomes usually resolve within approximately 4 weeks; however, in the untreated patient, the associated pain, or post-herpetic neuralgia, can persist for several months or even years and can be a serious disabling condition, particularly in the elderly[5-7]. The pain is often accompanied by abnormal sensations such as allodynia, tingling or numbness[8]. Replication of VZV in the ganglion of the involved nerve results in destructive inflammation and/or nerve dysfunction[7,9].

The pharmacotherapy of herpes zoster comprises antivirals and analgesics. Tricyclic antidepressants (amitriptyline, desipramine), gabapentin, pregabalin and opioids are used to treat significant persistent pain[8,10].

Materials and Methods:

A prospective study was carried out to assess to efficacy and safety of valacyclovir versus acyclovir in the treatment of Herpes Zoster. The study was conducted in the Dept. of Dermatology and

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Venereology, Faridpur Medical College Hospital, Faridpur, Bangladesh from July 2015 to December 2016. Patients aged 18 years or older, who were otherwise healthy, and presented with clinically diagnosed localized herpes zoster within 72h after the onset of rash were included in this study. Acute herpes zoster was clinically diagnosed who met the criteria for enrollment based on the presence of unilateral dermatomal rash. A total of fifty (50) patients were enrolled in the study after taking an informed consent. Patients with pregnancy, lactating mothers, treated with other antiviral medications and immunomodulator agents, patients with preexisting renal & hepatic impairment and known immunocompromised status were excluded from the study. Relevant data were taken and they were randomized into 2 groups of 25 each to receive either valacyclovir 1000 mg three times or acyclovir 800 mg five times per day for 7 days each orally. Patients were followed up on day 7, 14, 22 and 29 and assessed for the efficacy and safety.

To assess the effect of the drugs on healing of the rash, the proportion of patients having completely healed rash and occurrence of any new lesion formation was recorded. Presence of complications of Zoster, if any was recorded at each visit. Assessment of intensity of pain was done using visual analog scale (VAS) which is a numerical rating scale marked from 0 to 10 in increasing order of severity. A score of 0 was described as no pain and 10 as worst possible pain. The patients were instructed to use the scale from left to right and place a mark on the scale depending on the severity by pain perceived by them. The reduction in mean pain scores, the proportions of patients without pain and presence of abnormal sensations were compared between the two groups during each visit.

Statistical analysis was conducted using SPSS Software, data was analyzed descriptively mann whither V test was applied to compare mean VAS scores between the groups. Patients with presence of abnormal sensations and the proportion of patients with completely healed rash were analyzed by chi-square test. A P Value of <0.005 was considered significant.

Results:

Majority of the patients in both the groups were in 20-59 years. The mean age ± SD was 43.1 ± 15.61 and 43.08 ± 16.27 in the valacyclovir and acyclovir group respectively which was not statistically significant (Table-I).

Table-I: Distribution of patients according to age.

Age in Years	Valacyclovir No. of Patients (%)	Acyclovir No. of Patients (%)
<20	1 (4)	1 (4)
20-39	10 (40)	9 (36)
40-59	10 (40)	10 (40)
60-79	4 (16)	5 (20)
Total	25 (100)	25 (100)
Mean ± SD	**43.1 ± 15.61**	**43.08 ± 16.27**

The gender wise distribution was comparable for both the groups. Male patients were predominant in both the groups (Table-II).

Table-II: Distribution of patients according to sex.

Gender	Valacyclovir No. of Patients (%)	Acyclovir No. of Patients (%)
Male	20 (80)	22 (88)
Female	5 (20)	3 (12)
Total	**25** (100)	**25** (100)

In most of the patients the duration of rash was 72h.The mean duration of rash was comparable ± 16.79h and ± 15.8h for valacyclovir and acyclovir respectively (Table-III).

Table-III: Comparison of duration of rash at presentation

Duration of rash (hours)	Valacyclovir No. of patients (%)	Acyclovir No. of patients (%)
24	3 (12)	2 (8)
48	6 (24)	6 (24)
72	16 (64)	17 (68)
Mean ± SD	**60.48 ± 16.79**	**62.4 ± 15.18**

Most of the patients had severe rash at presentation with 16 patients in each group (Table-IV).

Table-IV: Severity of rash at baseline

Severity	Valacyclovir No. of patients (%)	Acyclovir No. of patients
Mild (<25 lesions)	2 **(8)**	4 **(16)**
Moderate (25-50 lesions)	7 **(28)**	5 **(20)**
Severe (>50 lesions)	16 **(64)**	16 **(64)**

Most of the patients had severe rash at presentation with 16 patients in each group (Fig-1).

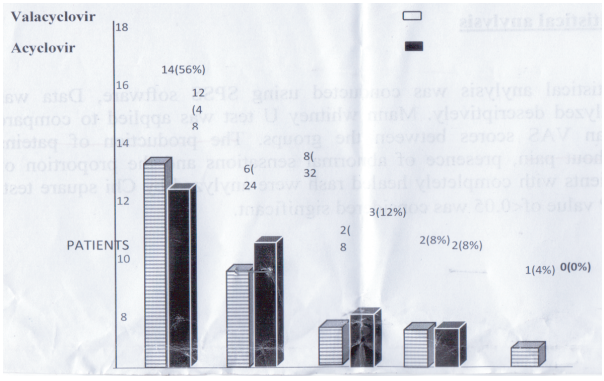

Fig-1: Symptomatic presentation of the patients.

All patients had pain at presentation. Pain was described in descending order of frequency as burning (56%, 48%), pricking (24%, 32%), stabbing (8%, 12%), shooting (8%, 8%), and throbbing (4%, 0%) in both the groups (Figure-I).

The comparison of VAS scores between valacyclovir and acyclovir at each follow up which were significantly reduced in valacyclovir group at day 22 (P=0.016) and 29 (P<0.001) compared to acyclovir group (Table-V).

Table-V: Comparison of VAS scores between groups

Day	Valacyclovir Vas Score Mean ± SD	Acyclovir Vas Score Mean ± SD	P Value
Do	6.46 ± 1.38	6.43 ± 1.50	o.976
D7	2.13 ± 1.56	2.96 ± 1.84	o.o78
D14	1.20 ± 1.44	2.06 ± 1.92	o.o59
D22	0.63 ± 0.92	1.63 ± 1.65	0.016*
D29	0.16 ± 0.46	1.10 ± 1.18	<0.001*

Tests Carried out by Mann Whither U test.

Abnormal sensations like pruritus, allodynia and paresthesias were present in 15(60%) and 14(56%) patients at baseline in the valacyclovir and acyclovir group respectively. At Day 29, only 2 and 3 patients in the valacyclovir and acyclovir group respectively had abnormal sensation which was not statistically significant (Table-VI).

Table-VI: Comparison of patients with zoster associated abnormal sensations.

Day	Valacyclovir No. of patients (%)	Acyclovir No. of patients (%)	P Value*
Do	15 (60)	14 (56)	0.082
D7	13 (52)	11 (44)	0.3209
D14	7 (28)	6 (24)	0.039
D22	3 (12)	4 (16)	0.166
D29	2 (8)	3 (10)	0.22

*Tests carried out by Chi square test, df=1.

A higher number of patients in the valacyclovir group (16) compared to acyclovir group (12) had completely healed rash at day 14 (P>0.05). Healing was complete in all 25 (100%) patients in valacyclovir group and 24 (96%) in acyclovir group on day 22 and 29 which was not statistically significant (Table-VII).

Table-VII: Comparison of healing of rash between groups

Day	Valacyclovir No. of patients (%)	Acyclovir No of patients (%)	P Value*
D7	1 (4)	0 (0)	_
D14	16 (64)	12 (48)	1.299
D22	25 (100)	24 (96)	1.020
D29	25 (100)	24 (96)	1.020

*Tests carried out by Chi square test, df=1.

A Total of 7 (28%) patients in valacyclovir group and 11 (44%) in acyclovir group developed complications of herpes zoster. Secondary bacterial infection occurred in 5 (20%) patients in valacyclovir group and 8 (32%) in acyclovir group. An ocular complication in the form of conjunctivitis was seen in 1 (4%) in valacyclovir group and 2 (8%) in acyclovir group, while keratitis occurred in 1 patient each in both the groups (Table-VIII).

Table-VIII: Comparison of patients with complications.

Complication	Acyclovir No. of patients (%)	Valacyclovir No. of patients (%)
Secondary bacterial infection	5 (20)	8 (32)
Conjunctivitis	1 (4)	2 (8)
Keratitis	1 (4)	1 (4)
Total	7 (28)	11 (44)

All the adverse events were mild in nature and involved 5 (20%) patients in both the groups (Table-IX).

Table-IX: Comparison of adverse events.

Adverse events	Valacyclovir No. Of Patients (%)	Acyclovir No. of Patients (%)
Nausea/ vomiting	2 (8)	2 (8)
Abdominal pain	1 (4)	1 (4)
Diarrhoea	_	1 (4)
Headache	2 (8)	1 (4)
Total	5 (20)	5 (20)

Discussion:

Pain is the most debilitating feature of herpes zoster[7,9,11,12]. Majority of the patients experienced pain immediately before and during the acute rash phase. Persistence of pain after rash healing may occur more commonly in the elderly and result in Post Herpetic Neuralgia (PHN) which is difficult and often costly to treat effectively[13]. So it is more important to prevent or reduce the possibility of persistent pain[14]. In the current study, analysis of the zoster associated pain showed significantly better pain resolution in the Valacyclovir group than in the Acyclovir group, and this trend persisted throughout the study period. In a multicenter (1141 patients) trial, Beutner et al[14] demonstrated that valacyclovir for 7 days significantly shortened the duration of herpes-zoster associated pain ($P<0.005$) compared with acyclovir; and the median time to cessation of pain for valacyclovir and acyclovir was 38 days and 51 days, respectively. As a result, patients treated with valacyclovir had a more satisfactory outcome in pain control than those treated with acyclovir. In this study, treatment effect in the valacyclovir group was slightly superior to that of the acyclovir group according to direct assessment of the rash. An increased acute pain and rash severity are risk factors of PHN. At presentation, majority of the patients had maculopapular rash with vesicles in the valacyclovir and acyclovir group respectively. In most of the patients, duration of rash was 72h. Most of the patients had severe rash at presentation with 16 patients in each groups. This finding is similar to results from other studies[15-18]. To achieve the same level of therapeutic effect, acyclovir needs to be taken five times (total 4 gm) daily ; however, valacyclovir needed to be taken only three times (total 3 gm) daily. Valacyclovir gets rapidly converted to acyclovir after oral administration via intestinal and hepatic metabolism, resulting in serum levels that are three to five times greater than those achieved with oral acyclovir and approximate those achieved with intravenous acyclovir administration. This may account for the faster resolution of pain with valacyclovir mainly due to its enhanced bioavailability of 54% compared to 20% for acyclovir[19]. The more convenient dosing profile of Valacyclovir results in better patient compliance and a lower incidence of adverse events[7,9,11,12]. The safety profile of acyclovir has been carefully established during more than 29 years of clinical use. In the current study, there were no clinically significant differences in the nature, frequency, or severity of adverse events between the two treatment groups.

Conclusion:

This study demonstrates that the administration of valacyclovir three times daily is an effective and safe treatment for acute herpes zoster. Valacyclovir treatment has the benefits of rapid resolution of the signs and symptoms of the herpes Zoster and an equivalent safety profile to acyclovir. Furthermore, using valacyclovir has the convenience of a three-times daily dosing, thereby ensuring better patient compliance, which makes this regimen an excellent choice for the treatment of herpes zoster.

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