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Research article

Comparative study of the efficacy of valacyclovir and acyclovir in herpes zoster

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ABSTRACT

In the present research work, the efficacy and safety of valacyclovir in comparison with acyclovir in the treatment of acute herpes zoster was investigated. Relevant data were taken from 60 patients with herpes zoster who presented within 72 h of the onset of rash and were randomized into two groups of 30 each. The first group received valacyclovir 1000 mg three times a day for 7 days while those in the second group received acyclovir 800 mg five times a day for 7 days respectively. Patients were followed up on day 3,8,15 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. When pain scores between the groups were compared, a significant decrease was observed with valacyclovir at day 22 ($P = 0.016$) and 29 ($P < 0.001$). Valacyclovir also significantly accelerated the resolution of zoster associated pain compared with acyclovir at day 29 ($P = 0.001$). The rate of cessation of abnormal sensations, rash healing, new lesion formation and complications 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. In the management of herpes zoster, valacyclovir accelerates the resolution of pain and offers a simpler dosing regimen and maintains the favorable safety profile of acyclovir.

Key words: Valacyclovir, Acyclovir, herpes zoster

1. 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 [1,2]. As reactivation of the virus is linked to diminished virus specific immunity, it develops mainly in the elderly and immunocompromised patients [3].

Pain is the most common complaint for which patients with herpes zoster seek medical care and therapy for zoster must alleviate the early symptoms and favorably affect outcome on chronic pain and postherpetic neuralgia (PHN) [4,5].

The pharmacotherapy of herpes zoster comprises of antivirals (given within 72 h of onset of rash), and analgesics. Tricyclic antidepressants (TCA's) (amitriptyline, desipramine), gabapentin , pregabalin and opioids are used to treat significant persistent pain [6,7].

2. MATERIALS AND METHODS

A prospective study was conducted on patients with herpes zoster attending Department of Dermatology at R.L. Jalappa Hospital and Research Centre, attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

2.1 Data collection

A proforma containing detailed information on each patient was prepared according to the protocol designed for the study. Informed consent was taken from all the patients

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included in the study. Ethical clearance was obtained from the institutional ethics committee.

2.2 *Selection criteria for patients*

A total of 60 patients with herpes zoster were enrolled in the study. Herpes zoster was diagnosed clinically based on the presence of tense, grouped, vesiculo bullous lesions on an erythematous base, unilaterally in a dermatomal distribution [8].

The inclusion criteria for the patients are:

1. patients above 18 years of age with clinical diagnosis of herpes zoster
2. new, untreated cases of herpes zoster
3. presentation within 72 h of onset of zoster rash

The exclusion criteria for the patients are:

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.

Relevant data was taken from the patients and they were randomized into 2 groups of 30 each to receive either valacyclovir 1000 mg three times or oral acyclovir 800 mg five times per day for 7 days each [9,10,11]. Patients were followed up on day 3, 8, 15, 22 and 29 and assessed for the efficacy and safety. The rash was defined depending on the different stages of lesions as follows:

1. *Maculopapular*: Reddened and/or raised above the surface of the surrounding skin; solid and not containing fluid.
2. *Vesicular*: Blister like, rise above the surface of the surrounding skin and containing fluid. It included pustules, which contain cloudy or darkened fluid and ulcers which may be present when the roof of the vesicle is lost.
3. *Crusted*: Dry, scab like layer that forms after the vesicular fluid is lost. It also included ulcers which may be present after the crust is lost, before re-epithelialization occurs.
4. *Healed*: Dry, non glistening, re-epithelialized skin after falling of crust. Erythema and scarring may be present.

Severity of rash was graded depending on the number of lesions as mild (<25 lesions), moderate (25-50 lesions) and severe (>50 lesions). 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 [12]. The patients were instructed to use the scale from left to right and place a mark on the scale depending on the severity of pain perceived by them. The reduction in mean pain scores, the proportion of patients without pain and presence of abnormal sensations was compared between the two groups during each visit. Patients with intolerable pain were prescribed analgesics which were recorded for both the groups.

2.3 Statistical analysis

Statistical analysis was conducted using SPSS software version 11. Data was analyzed descriptively. Mann Whitney U test was applied to compare mean VAS scores between the groups. The proportion of patients without pain, presence of abnormal sensations and the proportion of patients with completely healed rash were analyzed by Chi square test. A P value of < 0.05 was considered significant.

3. RESULTS

Majority of the patients in both the groups were in 20 – 59 years. The mean age ± SD was 43.56 ± 14.27 and 43.8 ± 13.17 in the valacyclovir and acyclovir group respectively which was not statistically significant (Table 1).

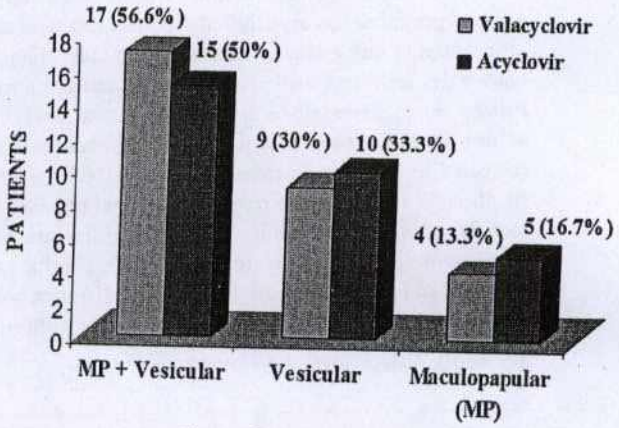

Fig.1 Morphology of rash at presentation

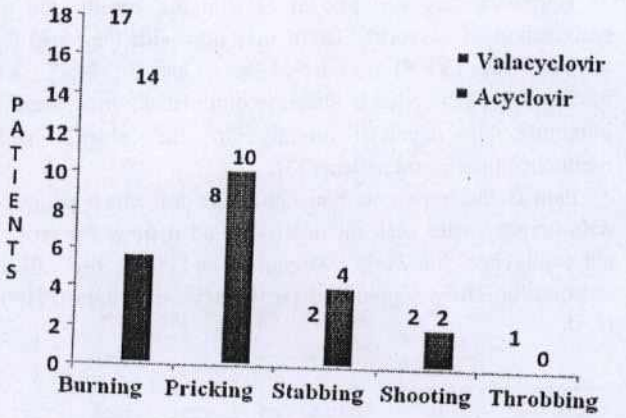

Fig.2 Pain character

Table 1
Age distribution

Age in years	Valacyclovir		Acyclovir	
	No.	%	No.	%
< 20	1	3.3	1	3.3
20-39	12	40	13	43.3
40-59	12	40	12	40
60-79	5	16.7	4	13.4
Total	30	100	30	100
Mean ± SD	43.56 ± 14.27		43.8 ± 13.17	

Table 2
Gender wise distribution of patients

Gender	Valacyclovir		Acyclovir	
	No.	%	No.	%
Male	23	76.7	22	73.3
Female	7	23.3	8	26.7
Total	30	100.0	30	100.0

Table 3
Dermatomal distribution

Distribution	Valacyclovir	Acyclovir
Thoracic	18 (60%)	17 (57%)
Cervical	6 (20%)	7 (23%)
Trigeminal	3 (10%)	4 (13%)
Lumbar	3 (10%)	2 (7%)

Table 4
Comparison of duration of rash at presentation

Duration of rash (h)	Valacyclovir		Acyclovir	
	No. of patients	%	No. of patients	%
24	3	10	2	6.7
48	9	30	8	26.7
72	18	60	20	66.6
Mean ± SD	60 ± 16.37		62.4 ± 14.91	

Table 5
Severity of rash at baseline

Severity	Valacyclovir		Acyclovir	
	No.	%	No.	%
Mild (<25 lesions)	3	10.0	4	13.3
Moderate (25-50 lesions)	10	33.3	9	30.0
Severe (>50 lesions)	17	56.7	17	56.7

Table 6
Comparison of vas scores between groups

Day	Valacyclovir VAS Score		Acyclovir VAS Score		P value
	Mean	SD	Mean	SD	
0	6.46	1.38	6.43	1.50	0.976
3	4.20	1.18	4.53	1.25	0.444
8	2.13	1.56	2.96	1.84	0.078
15	1.20	1.44	2.06	1.92	0.059
22	0.63	0.92	1.63	1.65	0.016*
29	0.16	0.46	1.10	1.18	< 0.001*

* P < 0.05 is significant

The gender wise distribution was comparable for both the groups. Male patients were predominant in both the groups (Table 2). The dermatomal distribution was similar in both the treatment groups. Thoracic dermatomal involvement was the commonest with 18 (60%) and 17 (57%) followed by cervical 6 (20%) and 7 (23%), trigeminal 3 (10%) and 4 (13%) and lumbar 3 (10%) and 2 (7%) in the valacyclovir and acyclovir groups respectively (Table 3). At presentation, majority of the patients - 17 (56.6%) and 15 (50%) had maculopapular rash with vesicles followed by vesicular 9 (30%) and 10 (33.3%), maculopapular 4 (13.3%) and 5 (16.7%) in the valacyclovir and acyclovir group respectively (Fig.1). In most of the patients, the duration of rash was 72 h. The mean duration of rash was comparable ± 16.37 h and ± 14.91 h for valacyclovir and acyclovir respectively (Table 4). Most of the patients had severe rash at presentation with 17 patients in each group (Table 5).

All patients had pain at presentation. Pain was described in descending order of frequency as burning , pricking (26.6% and 30%), stabbing (6.6% and 13.3%), shooting (6.6% and 6.6%) and throbbing (3.3% and 0%) in both the groups (Fig.2). 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 6). A greater number of patients were totally free from zoster associated pain at day 29 i.e. 26 (86.7%) compared to 14 (46.7%) in the valacyclovir and acyclovir group respectively which was statistically significant (P = 0.001) (Table 7).

Abnormal sensations like pruritus, allodynia and paresthesias were present in 18 (60%) and 17 (56.7%) patients at baseline in the valacyclovir and acyclovir group respectively. At day 29, only 2 and 3 patients in the

Table 7
Comparison of patients without zoster associated pain

Day	Valacyclovir		Acyclovir		P value
	No.	%	No	%	
Day 3	0	0	0	0	-
Day 8	8	26.7	4	13.3	0.197
Day 15	16	53.3	11	36.7	0.194
Day 22	19	63.3	13	43.3	0.121
Day 29	26	86.7	14	46.7	0.001*

* P < 0.05 is significant

Table 8
Comparison of patients with zoster associated abnormal sensations

Day	Valacyclovir		Acyclovir		P value
	No.	%	No	%	
0	18	60.0	17	56.7	0.793
3	15	50.0	13	43.3	0.605
8	16	53.3	13	43.3	0.438
15	8	26.7	7	23.3	0.766
22	4	13.3	5	16.7	0.766
29	2	6.7	3	10.0	0.640
% change	88.8	82.3	-		

valacyclovir and acyclovir group respectively had abnormal sensations which was not statistically significant.(Table 8) A higher number of patients in the valacyclovir group (19) compared to acyclovir group (15) had completely healed rash at day 15 (P = 0.297).Healing was complete in all 30 (100%) patients in valacyclovir group and 29 (96.7%) in acyclovir group on day 22 and day 29 which was not statistically significant (Table 9). Only 1 (3.3%) patient in valacyclovir group and 2 (6.6%) in acyclovir group developed new lesions on day 3 which was not statistically significant (Table 10).

A total of 3 (10%) patients in valacyclovir group and 4 (13.3%) in acyclovir group developed complications of herpes zoster. Secondary bacterial infection occurred in 2 (6.6%) patients in valacyclovir group and 3 (10%) in acyclovir group. An ocular complication in the form of conjunctivitis was seen in 1 (3.3%) patient each in both the groups while Keratitis occurred in 1 patient in acyclovir group (Table 11). All the adverse events were mild in nature and involved 3 (10%) patients in both the groups (Table 12).

Table 9
Comparison of healing of rash between groups

Day	Valacyclovir		Acyclovir		P value
	No.	%	No.	%	
3	0	0	0	0	-
8	1	3.3	0	0	-
15	19	63.3	15	50	0.297
22	30	100	29	96.7	0.313
29	30	100	29	96.7	0.313

Table 10
Comparison of patients with new lesion formation

Day	Valacyclovir	Acyclovir
	No.	No.
3	1 (3.3%)	2 (6.6%)
8	-	-
15	-	-
22	-	-
29	-	-

Table 11
Comparison of patients with complications

Complication	Valacyclovir	Acyclovir
Secondary bacterial infection	2 (6.6%)	3 (10%)
Conjunctivitis	1 (3.3%)	1 (3.3%)
Keratitis	-	1 (3.3%)
Total	3 (10%)	4 (13.3%)

Table 12
Comparison of adverse events

Adverse event	Valacyclovir	Acyclovir
Nausea	1 (3.3%)	-
Nausea + Vomiting	1 (3.3%)	1 (3.3%)
Abdominal pain	-	1 (3.3%)
Diarrhea	-	1 (3.3%)
Headache	1 (3.3%)	-
Total	3 (10%)	3 (10%)

4. DISCUSSION

Acute herpes zoster is a painful, debilitating condition. It occurs due to reactivation of VZV from a latent infection of dorsal sensory or cranial nerve ganglia. Declining cell mediated immunity as a result of aging, immunosuppressive illnesses and immunosuppressive agents increase the risk of zoster [2].

The pain of herpes zoster is the principal reason most patients seek medical attention [4]. Persistence of pain after rash healing may occur more commonly in the elderly and result in PHN which is difficult and often costly to treat effectively [4]. Antiviral therapy has been shown to decrease the duration of herpes zoster and the severity of pain associated with rash [13]. 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 PHN.

The oral nucleoside analogue, acyclovir, is widely used in the treatment of herpes zoster. The analogue, valacyclovir has been claimed to accelerate the resolution of zoster associated pain better than acyclovir and also decrease the percentage of patients with PHN [14]. In the present study, we have compared the efficacy of valacyclovir 1000 mg three times daily with acyclovir 800 mg five times daily given for a period of 7 days in the treatment of acute herpes zoster. The parameters assessed were pain scores using visual analog scale, presence of abnormal sensations like pruritus, allodynia and paresthesias, rash healing. When VAS scores between the treatment groups were compared, valacyclovir had a mean score of 0.63 ± 0.92 ($P = 0.016$) on day 22 and 0.16 ± 0.46 ($P < 0.001$) on day 29 which was statistically significant. Two patients in each group required additional analgesia with diclofenac 50 mg two times a day for 3 days.

On day 29, 26 (86.7%) and 14 (46.7%) patients were totally pain free in the valacyclovir and acyclovir respectively which was statistically significant ($P < 0.001$).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. The percentage decrease in cessation of abnormal sensations from baseline to the end of the study period was 88.8% and 82.8% for valacyclovir and acyclovir respectively which was not statistically significant. On day 15, 63.3% and 50% and on day 29, 100% and 96.7% patients had completely healed rash in the valacyclovir and acyclovir group respectively which was not statistically significant. Healing was not related to severity of rash at baseline as nearly all patients had healed rash at the end of the study period.

New lesion formation, a surrogate marker for ongoing viral replication was effectively reduced by both the treatments. However, 1 (3.3%) and 2 (6.6%) patients in valacyclovir and acyclovir group respectively had new lesion formation at day 3 only. No new lesion formation occurred in either group thereafter. The commonest complication to occur was secondary bacterial infection, 2 (6.6%) patients in

valacyclovir group and 3 (10%) in acyclovir group. Ocular complications of herpes zoster ophthalmicus was seen in 1 (3.3%) and 2 (6.6%) patients in the valacyclovir and acyclovir group respectively. Both the treatments had a favorable outcome on ocular complications. To achieve the same level of therapeutic effect, acyclovir needs to be taken five times (total 4 g) daily while valacyclovir needed to be taken only three times (total 3 g) 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 [11]. This may account for the faster resolution of pain with valacyclovir mainly due to its enhanced bioavailability of 54% compared to 20% for acyclovir [15,11]. The more convenient dosing profile of valacyclovir results in better patient compliance and may avoid suboptimal treatment of zoster and reduce the incidence of viral resistance. 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.

Valacyclovir caused more rapid resolution of zoster associated pain than acyclovir. Since greater severity of pain is an important risk factor for the development of PHN, valacyclovir may have a favorable outcome on PHN.

5. CONCLUSIONS

The results of the present study show that administration of valacyclovir 1000 mg three times a day is an effective and safe treatment for acute herpes zoster. Valacyclovir treatment has the benefits of rapid resolution of zoster associated pain and an equivalent safety profile to acyclovir. Furthermore, using valacyclovir has the convenience of three times daily dosing compared to five times daily dosing with acyclovir. This ensures better patient compliance and makes valacyclovir a better choice for the management of acute herpes zoster.

REFERENCES

[1] Wood, M.J., *Herpes* 2000, *7*, 60-65.

[2] Gnann, J.W., Whitley, R.J., *N Engl J Med* 2002, *347*, 340-346.

[3] Opstelten, W., Eekhof, J., Neven, A.K., Verheij, T., *Can Fam Physician* 2008, *54*, 373-377.

[4] Dworkin, R.H., Portenoy, R.K., *Pain* 1996, *67*, 241-225.

[5] Tyring, S.K., Beutner, K.R., Tucker, B.A., Anderson, W.C., Crooks, R.J., *Arch Fam Med* 2000, *34*, 138-142.

[6] Stankus, S.J., Dlugopolski, M., Packer, D., *Am Fam Physician.* 2000, *61*, 2437-2444.

[7] Johnson, R.W., *J Infect Dis* 2002, *186*, S83-90

[8] Klauswolff, Goldsmith, L.A., Katz, S.I., Gilchrest, B.A., Paller, S.A., Leffell, D.J. (Ed.). *Fitzpatricks Dermatology in General Medicine*, Mc Graw Hill 7th edition New York 2008, pp. 1891-1892.

[9] Hayden, F.G., in: Brunton, L.L., Lazo, J.S., Parker, K.L., (Eds.) *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th ed., Mc Graw Hill, New York 2006, pp.1243-1271.

[10] Vajpayee, M., Malhotra, N. *Indian J Pharmacol* 2000, *32*, 330-338.

[11] Safrin, S., in: Katzung, B.G. (Eds.). *Basic and Clinical Pharmacology*, 10th ed., Mc Graw Hill, New York 2007, pp.790-818.

[12] Dworkin, R.H., Gnann, J.W., Oaklander, A.L., Raja, S.N., Schmader, K.E., Whitley, R.J., *The Journal of Pain* 2008, *9*, S37-S44.

[13] Nikkels, A.F., Piérard, G.E. *Am J Clin Dermatol* 2002, *3*, 591-598.

[14] Beutner, K.R., Friedman, D.J., Forszpaniak, C., Andersen, P.L., Wood, M.J., *Antimicrob Agents Chemother* 1995, *39*, 1546-1553.

[15] Sweetman, S.C., in: Sweetman, S.C. (Ed.). *Martindale: The Complete Drug Reference* 35th ed., Vol. 1. Pharmaceutical Press, London 2007, pp.766-850.