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Comparative Study between Oral Valacyclovir and Oral Acyclovir in the Treatment of Herpes Zoster

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Abstract:

Background: Valacyclovir is an oral prodrug of acyclovir. It has a bioavailability 35 times greater than that of oral acyclovir. Moreover the convenient dose schedule as well as quicker cesation of post herpetic neuralgia makes valacyclovir more effacious than acyclovir in treating herpes zoster. So, the present study was planned to compare the efficacy and safety of oral valacyclovir over oral acyclovir in the treatment of herpes zoster. **Methods:** This was a clinical trial conducted in the outpatient department of Dermatology and Venereology at Shaheed Suhrawardy Medical College and Hospital, Dhaka between the period of April 2016 to September 2016. Sixty patients were selected according to the inclusion and exclusion criteria. All the patients were randomized into two groups. Group A as Valacyclovir (n=30) and group B as Acyclovir (n=30). Complete history was taken from the patient. Thorough clinical examination was done. Relevant investigations report was collected. All the informations were recorded in the fixed questionnaire. Collected data was classified, edited, coded and entered into the computer for statistical analysis by using SPSS-19. **Result:** Mean age was found 38.93±8.29 years in group A and 41.36±8.36 years in group B. 17 (56.7%) patients were male in group A and 16 (53.3%) in group B. Majority (56.7%) patients were thoracic in group A and group B respectively. In group A erythema, maculopapular rash, vesicle, bullae and crusting were present 29 (96.7%) cases, 28 (93.3%) cases, 22 (73.3%) cases, 22 (73.3%) cases and 14 (46.7%) cases respectively. In group B erythema, maculopapular rash, vesicle, bullae and crusting were present in 30 (100.0%) cases, 30 (100.0%) cases, 29 (96.7%) cases, 25(83.3%) cases and 17 (56.7%) cases respectively. Incidence of postherpetic neuralgia was found in 21 (70.0%) cases in group A and in 25 (83.3%) cases in group B. After 7 days treatment with valacyclovir in group A and acyclovir in group B, it was observed that symptoms and signs were reduced in both groups but more effectively in group A though the differences between the groups were statistically non-significant. However, it was observed that the patients of both groups showed similar remission pattern on 15th and 29th day. In baseline, mean pain scoring were 6.26±2.22 and 6.53±1.81 minutes in group A and group B respectively. At 3rd days, mean pain scoring was found 5.47±1.85 minutes in group A and 5.93±1.72 minutes in group B. At 8th days, mean pain scoring was found 4.23±1.50 minutes in group A and 5.13±1.45 minutes in group B. At 15th days, mean pain scoring was found 2.00±1.22 minutes in group A and 3.25±1.07 minutes in group B. At 22th days, mean pain scoring was found 0.76±0.74 minutes in group A and 1.75±0.95 minutes in group B. At 29th days, mean pain scoring was found 0.00±0.00 minutes in group A and 1.17±0.57 minutes in group B. The mean score at 8th, 15th, 22th days were statistically significant ($p<0.05$) between two groups. **Conclusion:** It can be concluded that administration of valacyclovir three times daily was an effective and safe treatment for acute herpes zoster. Treatment with valacyclovir has the benefits of rapid resolution of skin lesions, zoster associated pain, post herpetic neuralgia compared to acyclovir and valacyclovir has the convenience three times daily dosing, thereby ensuring better patient compliance, which makes this regimen an excellent choice for treatment of herpes zoster.

Indexing words: Herpes Zoster, Valacyclovir, Acyclovir

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Introduction:

Herpes Zoster remains an important medical problem throughout the world. It results due to reactivation of an earlier latent infection with the varicella zoster virus 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 patient.[3]

During the prodome of herpes zoster patient reports headache, photophobia and malaise, may be associated with fever. The disease begins with localized abnormal skin sensations ranging from itching, tingling to severe pain, which preceded the skin lesions by one to five days.[1] An erythematous maculopapular rash unilaterally distributed progresses to cluster of clear vesicles which continue to form 3 to 5 days and evolve through stages of pustulation, ulceration and crusting.[2] Healing occurs over a period of 2 to 4 weeks and often results in scarring and permanent changes in pigmentation. The cutaneous eruption is unilateral and does not cross the midline; lesions overlap adjacent dermatomes in 20% cases.[4]
Pain is the most common complaint for which patients with herpes zoster seek medical care.[5,6] Pain persisting after rash healing occurs in more than 50% of untreated patient and is the major complication of older patients.[7,8] The pain is often accompanied by abnormal sensations such as allodynia, tingling or numbness and decreases gradually over several months in most patient. Although some patients have pain persisting beyond 6 months.[8-10]

Post herpetic neuralgia (defined as pain that persists more than 30 days after the onset of rash or after cutaneous healing) is the most feared complication.[11] Both the incidence and the duration of postherpetic neuralgia are directly correlate with the patient's age.[12,14-16] The reported incidence of post herpetic neuralgia ranges from 8 to 70% and increased with age. In one study, the overall prevelance of post herpetic neuralgia was 8% after 30 days and 4.5% after 60 days.

In a number of previous studies treatment with valacyclovir 1000 mg three times daily for 7 days showed a significant advantage over treatment with acyclovir in reducing the duration of post herpetic neuralgia. Valacyclovir, the I-valyl ester of acyclovir is rapidly converted to acyclovir after oral administration and results that acyclovir bioavailability 3 to 5 times greater than that of oral acyclovir in human.[15,16] Biotransformation of valacyclovir to acyclovir is virtually complete after oral administration with each gram of valacyclovir yeilding approximately 700 mg of acyclovir and 300 mg of the essential amino acid valine. On the basis of this and preclinical studies, it was anticipated that the established safety profile of acyclovir would be retained with valacyclovir.[16]
The aim of the present study therefore was an attempt to evaluate the efficacy and safety of oral valacyclovir over acyclovir in the treatment of herpes zoster in different population of Bangladesh.

Method:
A randomized clinical trial was conducted among 60 patients of herpes zoster who attending in the outpatient department of Dermatology & Venereology at Shaheed Suhrawardy Medical College & Hospital, Dhaka during April 2016 to September 2016. Protocol of this study was approved by Ethical review committee of Shaheed Suhrawardy Medical College. Informed written consent was taken from each patient. All herpes zoster patients were recruited as per inclusion criteria who was randomly divided into two groups, 30 patients were treated with oral valacyclovir (group A) and the rest 30 patients with herpes zoster were treated with oral acyclovir (group B). Group A were treated with oral valacyclovir 1000 mg 3 times daily for 7 days and group B were treated with oral acyclovir 800 mg 5 times daily for 7 days and patients were followed up on day 3rd ,8th, 15th, 22th, 29th and assessed for the efficacy and safety by observing the clinical improvement and these data were recorded. The medicines were purchased by the patients himself or herself. Statistical analysis was carried out by using the Statistical Package for Social Sciences version 19.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous data. The quantitative observations were indicated by frequencies and percentages. Chi –Square test was used to analyze the categorical variables, shown with cross tabulation. Unpaired t-test was used for continuous variables. p values <0.05 was considered as statistically significant.

Results:
Mean age was found 38.93±8.29 years in group A and 41.36±8.36 years in group B. Seventeen (56.7%) patients were male in group A and 16(53.3%) in group B. Majority (56.7%) patients were thoracic in group A and group B respectively. The difference were not statistically significant (p>0.05) between these two groups (Table 1).

Table 1: Demographic characteristics of the study patients

Demographic characteristics	Group A (n=30)	Group B (n=30)	p value
Mean age (years)	38.93±8.29	41.36±8.36	[a]0.263[ns]
Sex:			
Male	17 (56.7%)	16 (53.3%)	[b]0.795[ns]
Female	13 (43.3%)	14 (46.7%)	
Types of herpes zoster:			
Thoracic	17 (56.7%)	17 (56.7%)	
Cervical	8 (26.7%)	9 (30.0%)	[b]0.787[ns]
Lumbosacral	4 (13.3%)	2 (6.7%)	
Trigeminal	1 (3.3%)	2 (6.7%)	

ns= not significant
[a]p value reached from unpaired t-test
[b]p value reached from chi square test
Group A= Valacyclovir
Group B= Acyclovir

Patients were selected randomly as group A and B randomly in alternate manner. After selection, In group A, erythema was present in 29(96.7%) cases, maculapapular rash present in 28(93.3%) cases, vesicle was present in 22 (73.3%) cases, bulla present in 22 (73.3%) cases and crusting was present in 14(46.7%) cases.
In group B, erythema was present in 30(100.0%) cases, maculopapular rash was present in 30(100.0%) cases, vesicle was present in 29(96.7%) cases, bulla was present in 25(83.3%) cases and crusting was present in 17(56.7%) cases (Table 2).

Table 2: Clinical findings of integumentary system of the study patients

Clinical findings of integumentary system	Group A (n=30)	Group B (n=30)
Erythema	29(96.7%)	30(100.0%)
Maculopapular rash	28(93.3%)	30(100.0%)
Vesicle	22(73.3%)	29 (96.7%)
Bulla	22(73.3%)	25 (83.3%)
Crusting	14(46.7%)	17 (56.7%)

After 7 days treatment with valacyclovir in group A and acyclovir in group B, it was observed that symptoms and signs were reduced in both groups but more effectively in group A though the differences between the groups were statistically non-significant (Table 3). However, from Table 4 and 5, it was observed that the patients of both groups showed similar remission pattern on 15th and 29th day.

Table 3: Distribution of patients according to observation and scoring at follow up on the 8th day, i.e. 7 days after initiating treatment

Observation and scoring at follow up	Group-A Valacyclovir	Group-B Acyclovir	p value
No new lesion	28 (93.3)	26(86.7)	0.671[b]
Reduction of erythema	26(86.7)	23(76.7)	0.317[a]
Reduction in size of involved area	29(96.7)	24(80.0)	0.103[b]
Reduction in pain severity score	17(56.7)	12(40.0)	0.493[a]

[a]Chi-square test was done to measure the level of significance
[b]Fisher's Exact test was done to measure the level of significance
Figure within parenthesis indicates in percentage

Table 4: Distribution of patients according to observation &scoring at follow up. This assessment was done on the 15th day, i.e. 14 days after initiating treatment

Observation and scoring at follow up	Group-A Valacyclovir	Group-B Acyclovir	p value
No new lesion formation	30(100.0)	30(100.0)	-
Reduction in erythema	30(100.0)	30(100.0)	-
Reduction in size of involved area	30(100.0)	29(96.7)	0.999[b]
Reduction in pain severity score	24(80.0)	20(66.7)	0.493[a]

[a]Chi-square test was done to measure the level of significance
[b]Fisher's Exact test was done to measure the level of significance
Figure within parenthesis indicates in percentage

Table 5: Distribution of patients according to observation &scoring at follow up. This assessment was done on the 29th day, i.e. 28 days after initiating treatment.

Observation and scoring at follow up	Group-A Valacyclovir	Group-B Acyclovir	p value
No new lesion formation	30(100.0)	30(100.0)	-
Reduction in erythema	30(100.0)	30(100.0)	-
Reduction in size of involved area	30(100.0)	30(100.0)	-
Reduction in pain severity score	30(100.0)	30(100.0)	-

Figure within parenthesis indicates in percentage

The presence of post herpetic neuralgia was more common in the acyclovir group than the valacyclovir group (83.3% vs 70.0%) but no significant difference (p=0.222) was found (Table 6).

Table 6: Incidence of post herpetic neuralgia of the study patients

	Group A (n=30)	Group B (n=30)	p value
29th day	21 (70.0%)	25 (83.3%)	0.222ns

ns= not significant
p value reached from chi square test

In baseline, mean pain score were 6.26±2.22 and 6.53±1.81 minutes in group A and group B respectively. At 3rd days, mean pain score was found 5.47±1.85 minutes in group A and 5.93±1.72 minutes in group B. At 8th days, mean pain score was found 4.23±1.50 minutes in group A and 5.13±1.45 minutes in group B. At 15th days, mean pain scoring was found 2.00±1.22 minutes in group A and 3.25±1.07 minutes in group B. At 22th days, mean pain score was found 0.76±0.74 minutes in group A and 1.75±0.95 minutes in group B. At 29th days, mean pain score was found 0.00±0.00 minutes in group A and 1.17±0.57 minutes in group B. The mean score at 8th, at 15th, at 22th days were statistically significantly lower (p<0.05) in group A than group B (Table 7).

Table 7: Pain score in different follow up day

Pain score	Group A (n=30)	Group B (n=30)	p value
Baseline	6.26±2.22	6.53±1.81	0.608ns
At 3rd day	5.47±1.85	5.93±1.72	0.323ns
At 8th day	4.23±1.50	5.13±1.45	0.022s
At 15th day	2.00±1.22	3.25±1.07	0.001s
At 22nd day	0.76±0.74	1.75±0.95	0.001s
At 29th day	0.00±0.00	1.17±0.57	-

s= significant, ns= not significant
p value reached from unpaired t-test

Discussion:

The study described the controlled investigation to date of antiviral agents for the treatment of herpes zoster. In this comparative study, it was demonstrated that treatment with valacylovir three times daily was effective in treating patients with herpes zoster.

The present study shows that among the total 60 patients, 33 (55%) were males and 27(45%) were females. Overall women may have a slightly greater risk of developing zoster when compared to men[17] but in this study males were more affected than females though the difference was not statistically significant (p=0.795).

The present study shows that mean age was found 38.93±8.29 years in group A and 41.36±8.36 years in group B. Usually the chance of developing herpes zoster increases with age as it is proved in previous studies.[18] As the subjects were selected randomly here the differences between the age group was not statistically significant (p=0.263).

In this series it was observed that thoracic involvement of herpes zoster was most common and 17(56.7%) patients in each group were found. Similar result observed in Soul-Lawton et al[19].

Skin lesions improved faster in patients on Valacyclovir compared to Acyclovir. An earlier study also noticed the faster resolution of skin lesion in Valacyclovir group but their findings were not statistically significant. Pain is the most common debilitating feature of herpes zoster.[19] The majority of patients experience pain immediately before and during the acute rash phase. However a more important clinical concern is to prevent or reduce the possibility of persistent pain.

The present study shows that the presence of post herpetic neuralgia was more common in the acyclovir group than the Valacyclovir group

(83.3% vs 70.0%) but difference was statistically not significant (p=0.222). However a large multicentre study found that the treatment with valacyclovir for 7 days significantly reduced the incidence of the post herpetic neuralgia compared to acyclovir.[18]

In baseline, mean pain score were 6.26±2.22 and 6.53±1.81 minutes in group A and group B respectively. At 3rd days, mean pain score was found 5.47±1.85 minutes in group A and 5.93±1.72 minutes in group B. At 8th days, mean pain score was found 4.23±1.50 minutes in group A and 5.13±1.45 minutes in group B. At 15th days, mean pain score was found 2.00±1.22 minutes in group A and 3.25±1.07 minutes in group B. At 22th days, mean pain score was found 0.76±0.74 minutes in group A and 1.75±0.95 minutes in group B. At 29th days, mean pain score was found 0.00±0.00 minutes in group A and 1.17±0.57 minutes in group B. The mean score at 8th, at 15th, at 22th days were statistically significant ($p<0.05$) between two groups. Valacyclovir recipients had a mean duration of 40 days of pain after lesion resolution compared to 60 days of pain after lesion resolution for acyclovir recipients. In terms of zoster related discomfort it is estimated that valacyclovir provides a 25% benefit over Acyclovir.[19] This study also shows that skin lesion and zoster associated pain improved significantly faster in the Valacyclovir group than Acyclovir.[18,19]

Safety profile of Acyclovir has been carefully established during >18 years of clinical use. In the present study there was no clinically significant difference in nature, frequency of severity, adverse events between the two treatment groups, as reported in earliest studies.[18,19]

Conclusion:

In conclusion, our study demonstrated that administration of Valacyclovir three times daily was an effective and safe treatment for acute herpes zoster. Treatment with Valacyclovir has the benefits of rapid resolution of skin lesions, zoster associated pain, post herpetic neuralgia compared to Acyclovir. Also Valacyclovir has the convenience three times daily dosing, thereby ensuring better patient compliance, which makes this regimen an excellent choice for treatment of herpes zoster.

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