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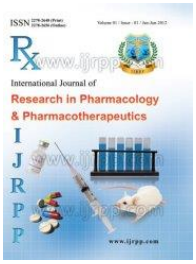

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Study of prescription pattern in the management of herpes zoster at brims hospital, bidar

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ABSTRACT

Aim & Objectives

1. To study the prescription patterns in Herpes Zoster cases in BRIMS Tertiary Hospital. 2. To assess the efficacy, tolerability and adverse drug reactions of the drugs used in treatment of Herpes Zoster.

Materials and Methods

This was a prospective study conducted on both outpatients and inpatients of BRIMS Tertiary Hospital, Bidar, from 11-8-2014 to 12-08-2015 on patients with herpes zoster attending Department of Dermatology. A total of 90 patients with herpes zoster who presented within 72 hours of the onset of rash were enrolled in the study and randomized into three groups of 30 each of whom 30 patients assigned Valacyclovir 1000 mg TID, 30 patients were assigned Acyclovir 800 mg five times a day and Famciclovir 250 mg BD for 7 days. The treatments were given for 7 days. Patients were periodically followed up till day 29 to assess the effect of the drugs on the rate of resolution of pain, cessation of abnormal sensations, rate of rash healing, new lesion formation and occurrence of complications.

Results

The pain scores (measured by VAS) between the groups were compared and a significant reduction was observed in Valacyclovir group day 22 ($P=0.013$) and day 29 ($P<0.0004$). A significantly greater proportion of patients in Valacyclovir group did not have Zoster associated pain at day 29 ($P=0.003$). All the three drugs showed significant reduction in pain scores within the group between 2 consecutive visits. This trend was persistent throughout the study period. The rate of cessation of abnormal sensations, rash healing, new lesions formation and occurrence of complications was similar in three groups. Adverse events were infrequent and mild in nature. Headache, nausea, vomiting and abnormal pain were reported which did not warrant discontinuation and withdrawal from the study.

Conclusion

In the management of HerpesZoster the reduction of pain was best with Valacyclovir better with Famciclovir and least in Acyclovir. Other than resolution of pain which is faster with Valacyclovir than compared to Acyclovir and Famciclovir, there is no difference in outcome of rash healing, abnormal sensation and adverse effect with three drugs.

Keywords: Valacyclovir, Acyclovir, Famciclovir, Herpes Zoster

INTRODUCTION

Safe and effective drug therapy mostly is possible only when patients are well informed about the medications and their use. [1] Rational drug use means patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community. [2] Confusion over brand names, overwhelming workload of doctors and pharmacists, cost factor, patient attitudes, erratic supply of drugs, lack of institutional formulary etc., can lead to irrational use of drugs. Irrational drug use can lead to reduction in quality of drug therapy, increased risk of unwanted effects, drug resistance etc. The five important criteria for rational drug use are accurate diagnosis, proper prescribing, correct dispensing, suitable packing and patient adherence.

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. [3] As reactivation of the virus is linked to diminished virus specific immunity, it develops mainly in the elderly and immunocompromised patients. [4] Pain is the most common complaint for which patients seek medical therapy and must alleviate the early symptoms and favourably affect outcome on chronic pain and postherpetic neuralgia (PHN). [5] The pharmacotherapy of herpes zoster comprises of antivirals (given within 72 hours of onset of rash), analgesics and corticosteroids. Tricyclic antidepressants (TCA‘s) (amitriptyline, desipramine), gabapentin or pregabalin and strong opioids are used to treat significant persistent pain. [6]

Antiviral agents have been shown to decrease the duration of herpes zoster rash and the severity of pain associated with the rash. [7] However, these benefits have only been demonstrated in patients who received antiviral agents within 72 hours after the onset of rash.

Acyclovir, the prototype antiviral drug, is a DNA polymerase inhibitor. Acyclovir may be given orally or intravenously. Major drawbacks of orally administered acyclovir include its lower bioavailability compared with other agents and its dosing frequency (five times daily).

Valacyclovir, a prodrug of acyclovir, is administered three times daily. Compared with acyclovir, valacyclovir may be better at decreasing the severity of pain as well as the duration of postherpetic neuralgia. [8]

Famciclovir has advantages of dosing schedule (three times daily), longer half-life compared with acyclovir and valacyclovir.

Orally administered corticosteroids in conjunction with acyclovir has been shown to reduce the pain by decreasing the degree of neuritis and residual damage to affected nerves. [9] Some studies designed to evaluate the effectiveness of prednisone therapy in preventing postherpetic neuralgia have shown decreased pain at 3 and 12 months. [10] [11] Other studies have demonstrated no benefit. [9] [12]

The pain in herpes zoster ranges may be mild to excruciating. Patients with mild to moderate pain may respond to over-the-counter analgesics. Patients with more severe pain may require the addition of a narcotic medication. When analgesics are used, with or without a narcotic, a regular dosing schedule results in better pain control and less anxiety. Lotions containing calamine (e.g., Caladryl) may be used on open lesions to reduce pain and pruritus. Topically administered lidocaine (Xylocaine) and nerve blocks have also been reported to be effective in reducing pain.

Therefore, the present study was undertaken to study the prescription patterns in management of Herpes Zoster and evaluate the efficacy, tolerability and adverse drug reactions of the drugs used in its treatment in BRIMS Tertiary Hospital.

AIM & OBJECTIVES

- To study the prescription patterns in Herpes Zoster cases in BRIMS Tertiary Hospital.
- To assess the efficacy, tolerability and adverse drug reactions of the drugs used in treatment of Herpes Zoster.

MATERIAL AND METHODS

Location of the study

This was a prospective study conducted on both outpatients and inpatients with herpes zoster attending Department of Dermatology at BRIMS Tertiary Hospital, Bidar, from 11-8-2014 to 12-08-2015.

Data collection

A proforma containing detailed information on each patient was prepared according to the protocol designed for the study. Prior permission to conduct the study was obtained from Institutional Ethics Committee (IEC) of BRIMS, Bidar. Informed consent was obtained from all patients their local language enrolled in the study.

INCLUSION CRITERIA

- ✓ Patients above 18 years of age with clinical diagnosis of herpes zoster.
- ✓ New, untreated cases of herpes zoster.
- ✓ Presentation within 72 hours of onset of zoster rash.

EXCLUSION CRITERIA

- ➢ Pregnant and nursing women.
- ➢ Patients treated with other antiviral medications and immunomodulatory agents.
- ➢ Known immunocompromised status.
- ➢ Patients with preexisting renal and hepatic impairment.

A total of 90 patients with herpes zoster were enrolled in the study and randomized into 3 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 or femciclovir 250 mg three times per day for 7 days each. Patients were followed up on day 3, 8, 15, 22 and 29 and assessed for the efficacy and safety of the three treatments.

Severity of rash was graded depending on the number of lesions as mild (<25 lesions), moderate (25-50 lesions) and severe (>50 lesions).

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. [13] The reduction in mean pain scores between and within the groups was analyzed.

Laboratory investigations included complete blood picture, blood sugar, blood urea, serum creatinine, HIV serology, chest X-ray, sputum examination and Tzanck smears as and when necessary.

STATISTICS

Data was analysed using SPSS software version 11 and descriptive statistics like percentages, proportions, Mean, Standard deviation were applied wherever necessary. One Way Analysis of Variation (ANOVA) test was applied to compare mean VAS scores between the groups. Efficacy of the treatments in reducing VAS scores within the groups over time was analysed by Wilcoxon sign ranks test. The proportion of patients without pain, presence of abnormal sensations and the proportion of patients with completely healed rash were analysed by Chi square test. A P value of < 0.05 was considered significant.

RESULTS

Majority of the patients were in 20 - 59 years age group. The mean age ± SD was 43.17 (±13.59), 42.47 (±14.4), 44.3 (±13.4) years in Valacyclovir, Acyclovir and Famciclovir groups respectively.

Table 1: Age Distribution

Age in years	Valacyclovir		Acyclovir		Famciclovir	
	Number	%	Number	%	Number	%
<20	1	03.3%	1	03.3%	2	06.6%
20-39	12	40.0%	11	36.7%	8	26.7%
40-59	12	40.0%	13	43.3%	15	50.0%
60-79	5	16.7%	5	16.7%	5	16.7%
Total	30	100%	30	100%	30	100%
Mean ±SD	43.17±13.59		42.47±14.4		44.3±13.42	

The gender wise distribution was comparable for all the three group. Males were predominant in all the groups. Comparatively, female proportion was highest in Acyclovir group (30%) and least in Famciclovir group (16.7%).

Table 2: Gender Wise Distribution of Patients

Gender	Valacyclovir		Acyclovir		Famciclovir	
	Number	%	Number	%	Number	%
Male	24	80%	21	70%	25	83.3%
Female	6	20%	9	30%	5	16.7%
Total	30	100%	30	100%	30	100%

The dermatomal distribution was similar in all the treatment groups. Thoracic dermatomal involvement was the commonest (57–63%), followed by cervical dermatomes (17-23%). Lumbar and trigeminal involvement was almost equal in Valacyclovir and Famciclovir groups (10% each) but in Acyclovir group trigeminal was more common (13%) than lumbar (6.7%).

Table 3: Distribution of Dermatomal Involvement

Dermatome	Valacyclovir		Acyclovir		Famciclovir	
	Number	%	Number	%	Number	%
Cervical	6	20%	7	23.3%	5	16.7%
Lumbar	3	10%	2	06.7%	3	10.0%
Thoracic	18	60%	17	56.7%	19	63.3%
Trigeminal	3	10%	4	13.3%	3	10.0%
Total	**30**	**100%**	**30**	**100%**	**30**	**100%**

In more than half of the patients in all the groups, the rash presented as maculopapular with vesicles, almost one-third of each group had vesicular rash and less than 20% had maculopapular rash at presentation.

More than half of the patients in each group had severe rash, with more than 50 lesions. Almost one third in each group had moderate rash, with 25 to 50 lesions. Very few in each group had mild rash at presentation.

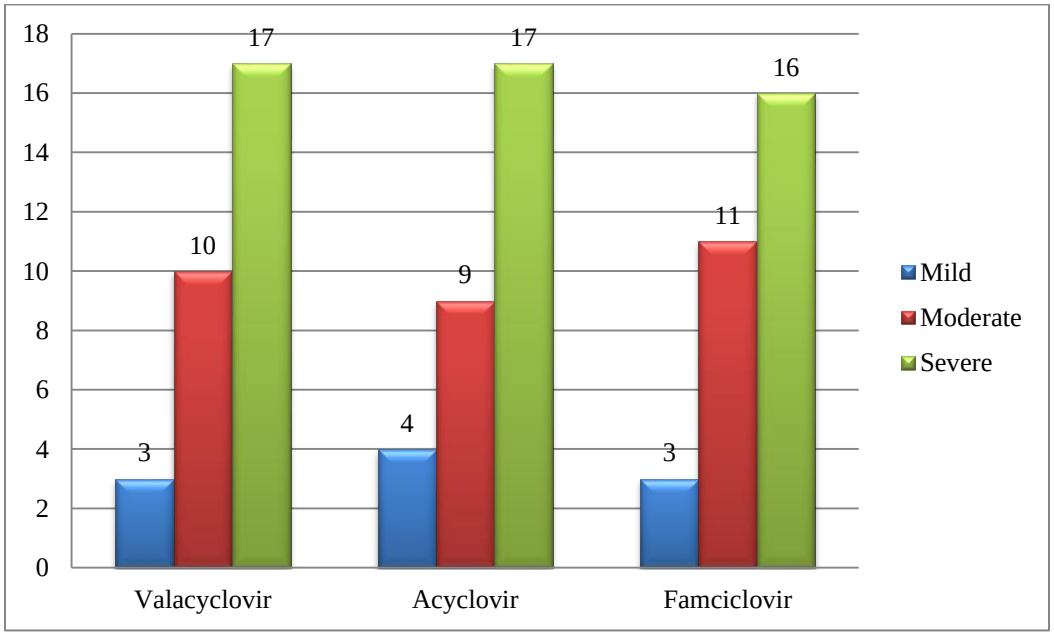

Figure.1: Severity of Rash At Presentation

In majority of the patients, the presentation was after 72 hours of onset of the rash (60% of Valacyclovir and Famcicyclovir groups and 66.6% of Acyclovir group).

All patients had pain at presentation. Most commonly, it was of Burning and pricking types in Valacyclovir, Acyclovir and Famciclovir groups. Very few patients complained of stabbing and shooting type. Throbbing type was complained only in Valacyclovir and Famciclovir groups.

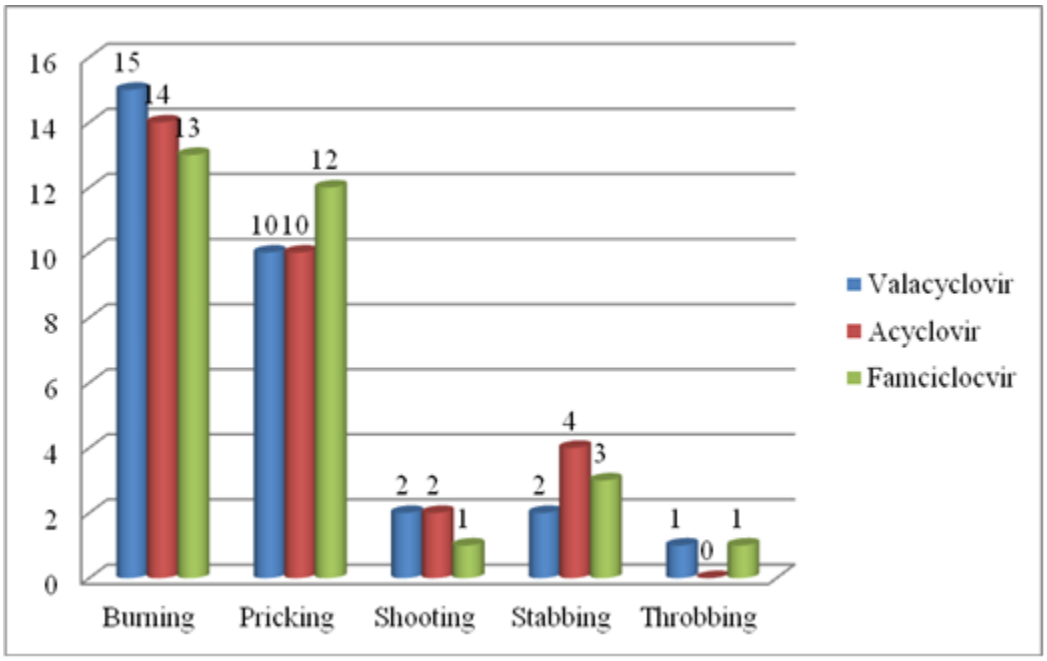

Figure.2: Pain Character at Presentation

The below table shows that the mean VAS scores have decreased over time in all the three groups. The efficacy to reduce pain among the three drugs was found to be best in Valacyclovir, better in Famciclovir and least in Acyclovir and this difference in efficacy was found statistically significant. On day 22, the mean VAS scores in Valacyclovir, Famciclovir and Acyclovir groups were 0.63, 1.23 and 1.57 respectively (p=0.013) and on day 29 the scores were 0.17, 0.63, 1.07 respectively (p=0.0004). This shows that Valacyclovir is better than Famciclovir and Famciclovir is better than Acyclovir in reducing the zoster related pain.

Table 4: Comparison of Vas Scores Between Groups

Day	Valacyclovir		Acyclovir		Famciclovir		p value**
	Mean	SD	Mean	SD	Mean	SD	
0	6.46	1.38	6.43	1.5	7.03	1.27	0.18
3	4.2	1.19	4.53	1.25	5.23	1.35	0.104
8	2.13	1.57	2.97	1.85	3.03	0.82	0.217
15	1.2	1.45	2.07	1.93	2.23	1.16	0.129
22	0.63	0.92	1.57	1.67	1.23	0.89	0.013*
29	0.17	0.46	1.07	1.2	0.63	0.72	0.0004*

*p <0.05 => statistical significance
**One way ANOVA test

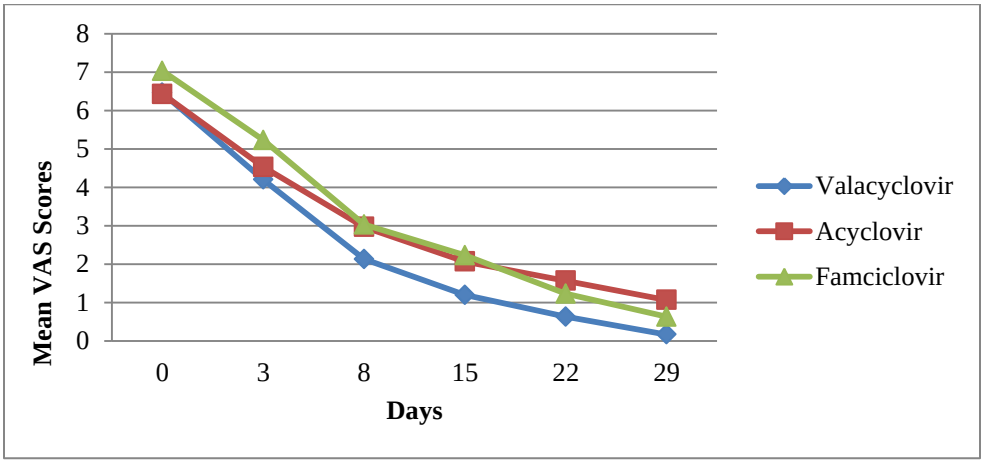

Figure.3: Comparision of Vas Scores Between Groups

As seen in the table, greater proportions of people attained zoster pain free status in Valacyclovir then in Famciclovir group and then in Acyclovir group at each day. These differences were statistically significant on day 15 (p= 0.001), day 22 (p=0.016) and day 29 (p=0.003). In other words, the pain free status is attained faster in Valacyclovir, fast in Famciclovir and comparatively late in Acyclovir group.

Table 5: Comparison of Patients Without Zoster Associated Pain

Day	Valacyclovir		Acyclovir		Famciclovir		p value**
	Number	%	Number	%	Number	%	
3	0	0%	0	0%	0	0%	--
8	8	26.7%	2	6.7%	4	13.3%	0.196
15	16	53.3%	3	10%	11	36.7%	0.001*
22	19	63.3%	8	26.7%	14	46.7%	0.016*
29	26	86.7%	15	50%	15	50%	0.003*

*p <0.05 => statistical significance

**Chi square Test

The mean reduction of VAS scores over time in each group and between each time period were found statistically significant. The amount of fall was higher initially and tapered over time in Valacyclovir and Acyclovir groups but fall was uneven in Famciclovir group.

Table 6: Reduction in Vas Scores within the Groups Over Time

Days compared	Valacyclovir		Acyclovir		Famciclovir	
	Decrease in means	P value**	Decrease in means	P value**	Decrease in means	P value**
0 & 3	2.26	<0.001*	1.9	<0.001*	1.8	<0.001*
3 & 8	2.07	<0.001*	1.57	<0.001*	2.2	<0.001*
8 & 15	0.93	0.001*	0.9	<0.001*	0.8	<0.001*
15 & 22	0.57	0.001*	0.5	0.001*	1.0	<0.001*
22 & 29	0.47	0.001*	0.5	0.001*	0.6	<0.001*

* p <0.05 => statistical significance

** Wilcoxon Sign Rank Test

Secondary bacterial infection was the most common complication noticed. 6.7% of Valacyclovir and Famciclovir groups and 10% each of Acyclovir group experienced complications. Ocular complication like conjunctivitis was also observed

Table 7: Comparison of Patients with Complications

Complication	Valacyclovir		Acyclovir		Famciclovir	
	Number	%	Number	%	Number	%
Conjunctivitis	0	0%	1	3.3%	1	3.3%
Sec Bacterial Infection	2	6.7%	2	6.7%	1	3.3%
Total	2	6.7%	3	10%	2	6.7%

No serious adverse effects were observed during the study. They included headache and gastro intestinal disturbances like nausea, vomiting, abdominal pain and diarrhoea.

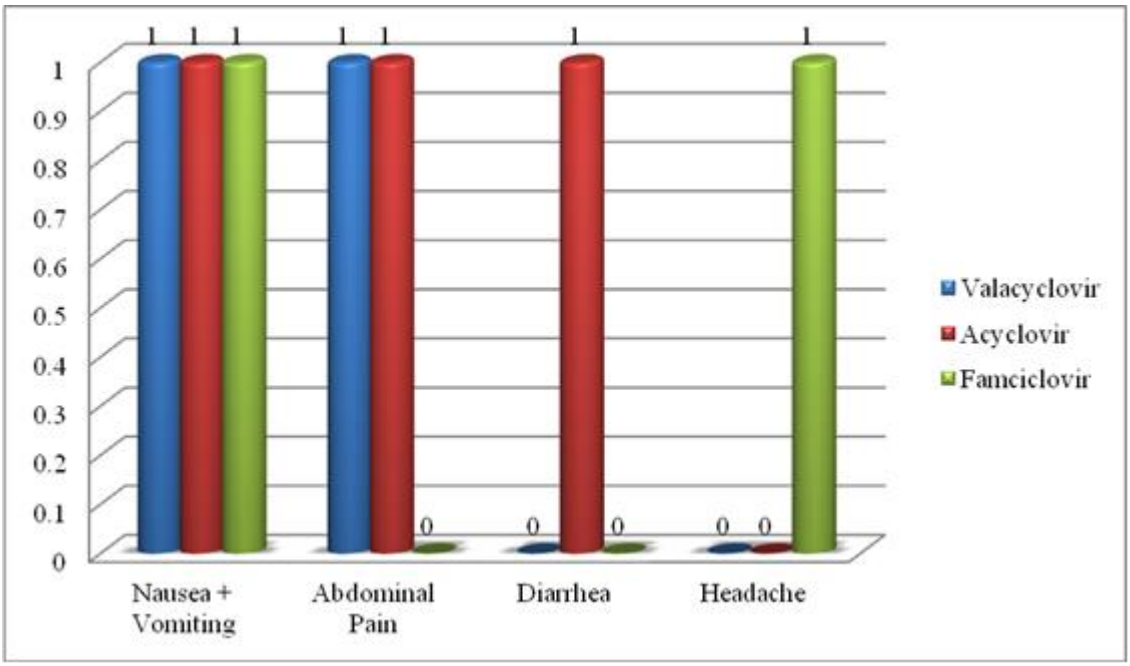

Figure.4: Adverse Effects

Paracetamol was prescribed along with the antivirals in 73.3% of the patients. Carbamezapine (63.3%), Methcobalamine (54.4%), Silverex ointment (48.9%), and Cetrizine (26.7%) were the other frequently co-prescribed drugs. Antibiotics like Azithromycin, Tobramycin, and other drugs like Mupirocin and Homatropine were also prescribed but sparsely.

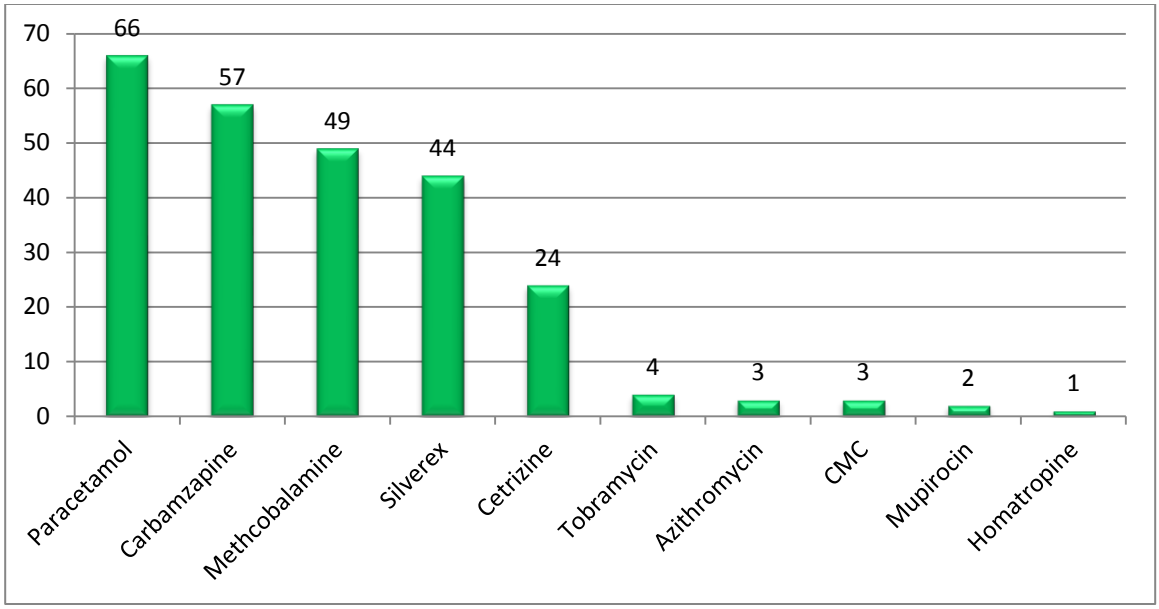

Figure.5: Prescription Pattern of Drugs

DISCUSSION

Acute herpes zoster is a painful, debilitating condition. It occurs due to reactivation of Varicella Zoster Virus (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. [3]

The pain of herpes zoster is the principal reason most patients seek medical attention. Persistence of pain after rash healing may occur more commonly in the elderly and result in Postherpetic Neuralgia (PHN) which is difficult and often costly to treat effectively. [5] 8 Antiviral therapy has been shown to decrease the duration of herpes zoster and the severity of pain associated with rash. [14]

The oral nucleoside analogue, acyclovir, is widely used in the treatment of herpes zoster. The newer analogue, valacyclovir, has been claimed to accelerate the resolution of zoster associated pain better than acyclovir and famciclovir also decrease the percentage of patients with PHN. [6] [15]

When Visual Analog Scale (VAS) scores between the treatment groups were Valacyclovir 0.63±0.92, Acyclovir 1.57±1.67, Famciclovir 1.23±0.89 with P=0.013. On day 22 and on day 29 Valacyclovir 0.17±0.46, Acyclovir 0.07±1.0 Famciclovir 0.63±0.72 P<0.0004, which was statistically significant.

The percentage reduction in VAS scores at end point was 97.37%, 83.36% and 91.04% Valacyclovir, Acyclovir and Famciclovir respectively.

Valacyclovir provided a faster resolution of pain with 8 (26.7%) patients becoming pain free at day 8, as compared to Acyclovir 2 (6.7%) and Famciclovir 4 (13.3%) which was not statistically significant (P=0.196). On day 29 Valacyclovir 26 (86.7%), Acyclovir 15 (50%) and Famciclovir 15 (50%), patients were totally pain free in the Valacyclovir, Acyclovir and Famciclovir respectively which was statistically significant (P<0.003).

Beutner et al., demonstrated that Valacyclovir significantly shortened the duration of Zoster associated pain compared to Acyclovir. [6]

Tyring et al., demonstrated that valacyclovir significantly shortened the duration of zoster associated pain compared to famciclovir. A significant decrease in mean VAS scores when compared to the previous scores was observed within the treatment groups for both the drugs. [15]

The commonest complication to occur was Secondary Bacterial Infection which is 2 (6.7%) in Valacyclovir group, 2 (6.7%) in Acyclovir group and 1 (3.3%) in Famciclovir group.

In the current study, Valacyclovir, Acyclovir and Famciclovir were well tolerated. There were no

clinically significant differences in the nature, and or severity of adverse events between the three groups.

The tolerability profiles of the three drugs were similar which is in accordance with Beutner KR, Tyring SK et al., Lin WR. [6][15][16] No serious adverse events were observed in either group to warrant with drawal from the study.

In the present study, Valacyclovir caused mere rapid resolution of Zoster associated pain than Acyclovir and Famciclovir. Since greater severity of pain is an important risk factor for the development of PHN, Valacyclovir may have a favorable outcome on PHN.

However, the present study was not designed to assess the effect of the drugs on PHN.

CONCLUSION

The results of the present study show that administration of Valacyclovir 1000 mg three times a day is an effective and safe in the treatment of Acute Herpes Zoster. Famciclovir 250 mg thrice daily is also effective and safe in the management of Acute Herpes Zoster. Furthermore, using Valacyclovir and Famciclovir has the convenience of three times daily as compared to Acyclovir five times daily dosing. This ensures better patient compliance and makes Valacyclovir and Famciclovir excellent drugs for the management of Acute Herpes Zoster.

The reduction of pain was best with Valacyclovir better with Famciclovir and least in Acyclovir. Other than resolution of pain which is faster with Valacyclovir than compared to Acyclovir and Famciclovir, there is no difference in outcome of rash healing, abnormal sensation and adverse effect with three drugs.

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