Original Article

The efficacy of time-based short-course acyclovir therapy in treatment of post-herpetic pain

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Abstract

Introduction: Various treatments have been used to manage post-herpetic neuralgia (PHN). Safe and effective therapies to prevent PHN are needed.

Methodology: A clinical trial involving 152 patients diagnosed with acute herpes Zoster (HZ) was conducted to determine whether short-course acyclovir therapy (800 mg five times a day for four days) can alleviate HZ-associated pain and prevent post-herpetic neuralgia (PHN). The patients were divided into two groups: Group 1 had a rash with a duration of less than 72 hours and Group 2 had a rash with a duration of more than 72 hours. To assess PHN, the patients categorized and assessed the severity of their symptoms using a four-point verbal rating scale (VRS).

Results: By the fourth week, 134 out of 152 patients (88.2%) had complete pain response (CPR). Of these, 68 patients (89.5%) were from Group 1 and 66 from Group 2 (86.8%). After four weeks, the mean VRS scores had changed significantly in both groups compared to the scores at the beginning of study ($p = 0.001$), but there was no difference between the two groups (0.88 ± 0.66 Vs. 0.94 ± 0.72; $p = 0.66$) After three months no differences were observed in the treatment results between the two groups (0.51 ± 0.13 Vs.0.54 ± 0.19; $p = 0.77$).

Conclusion: Short-course acyclovir therapy is an effective treatment for zoster and its efficacy in patients with a rash duration of more than 72 hours is similar to that in patients with rash duration of less than 72 hours.

Key words: Herpes zoster; short course therapy; post-herpetic neuralgia; acyclovir

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Introduction

Herpes zoster (HZ) is caused by reactivation of the Varicella-Zoster Virus (VZV), which remains latent in the sensory ganglia after primary infection [1]. During the acute illness, the rash is often accompanied by pain, and the most frequent complication of HZ infection is post-herpetic neuralgia (PHN), defined as debilitating pain, the pathogenesis of which remains unclear [2,3]. The true incidence of post-herpetic neuralgia is difficult to establish and depends partly on the definition being used. The incidence of PHN increases with advancing age [4,5].

Prevention of PHN is therefore an objective of most studies in the treatment of herpes zoster. Therapeutic interventions to avoid PHN include antiviral agents, corticosteroids, tricyclic antidepressants, and combinations of these [6]. An accurate estimate of the frequency, duration, and clinical importance of PHN after a single episode of herpes zoster would be helpful in interpreting studies on the prevention of PHN and in counselling patients about the risk of long-term pain after acute episodes of herpes zoster. Acyclovir, an analogue of 2′-deoxyguanosine, has been proved to have an *in-vitro* antiviral activity against VZV [7].Since its introduction to medical treatment in 1983, acyclovir has become the most widely prescribed antiviral drug in the world [8,9].

The benefits of acyclovir therapy during the acute phase of herpes zoster are established [10-13]. In

controlled trials, intravenous and oral doses of acyclovir in immunocompetent patients are associated with significant improvement in the rate of healing and severity of the acute pain of herpes zoster [6,10-13]. The effects of acyclovir on PHN are less clear-cut. Three studies comparing oral acyclovir with placebo [11-13] determined that the incidence of prolonged pain was lowered in acyclovir recipients. In contrast, some other studies which evaluated the effects of five to seven days of intravenous or oral acyclovir found no benefit with respect to prolonged pain [6,10]. Consequently, the efficacy of acyclovir after three days of zoster infection remains in doubt.

A selective controlled clinical trial was therefore designed to compare the efficacy of oral acyclovir in patients who presented within three days of the onset of Zoster rash to its efficacy in patients who presented with Zoster rash with a duration between three to seven days.

Methodology

Selection of patients

We conducted our clinical trial from January 2004 to January 2008 in the dermatology outpatient department of Hazrat-e-Rasul Akram Hospital, Tehran, Iran. The number of the patients with HZ which were included in this study was 152. Subjects were immunocompetent patients of either gender, aged 50 years and above, attending our departments for treatment of zoster. Patients who presented within the day of the onset of rash were enrolled in Group 1 (G1), and patients who presented after three days were enrolled in Group 2 (G2). The baseline clinical characteristics and disease severity were similar in both groups. The diagnosis of HZ was made on clinical criteria (painful coetaneous, dermatomal, unilateral, and papulo-vesicular lesions). Written consent to participate was obtained from each patient individually. The study was conducted in accordance with the principles stated in the Declaration of Helsinki and was approved by the ethics committee of the Iran University of Medical Sciences.

Adverse events, both local and systemic, or inter-current illness, were recorded at each visit and their relation to the trial drug was judged. Liver function tests were performed both at the first visit and at the end of the treatment period. We also performed urinary analysis and serum Creatinin (Cr) and Blood Urea Nitrogen (BUN) analysis each week to monitor for potential renal problems such as crystallization.

Patients received no other treatments for HZ throughout the study period. Clinical assessment in each visit was performed by a single dermatologist.

Assessment

The efficacy measurement in this study was the existence and severity of pain. Follow-up visits were performed at the first week, second week, first month and third month after the rash onset. Patients were asked to categorize and assess the severity of their symptoms using the following four-point verbal rating scale (VRS): 0 (no pain); 1 (mild pain that does not interfere with daily activities); 2 (moderate pain that interferes with daily activities but does not cause sleeplessness); 3 (severe pain that causes sleeplessness); or 4 (very severe unbearable pain that was extremely incapacitating) [14].

Acute HZ pain intensity response was scored by the patient and was defined as the following: (I) Mild pain after treatment indicated 75% improvement, and complete pain relief was classified as 100% improvement. This level of pain reduction was classified as Complete Pain Response (CPR). These patients had either no pain or mild pain and could sleep without analgesic. (II) Moderate pain reduction denoted 50% improvement and was considered Partial Pain Response (PPR). These patients had moderate pain and could sleep with simple analgesics. (III) No reduction of pain at all, or reduction of pain from very severe to severe, indicated 25% improvement and was considered No Pain Response (NPR). These patients had severe and intractable pain, and could not sleep even with strong analgesics.

Exclusion criteria

Patients who had received any systemic antiviral treatment within the four weeks preceding screening; subjects who were allergic to acyclovir or under treatment with drugs interacting with acyclovir; patients with liver or renal diseases; and patients with conditions that could interfere with gastrointestinal absorption of acyclovir were excluded from study.

Treatment regimens

All patients took acyclovir, 800 mg five times a day, for the first four days of the first week, followed by three treatment-free days. In the cases evidence of pain reduction but not CPR, a second course of treatment with the same dosage was offered. The patients were followed for three months without

medication. All patients were strictly advised not to use any topical or systemic drugs.

Clinical response evaluation

All patients were evaluated by a clinician as well as the patient's self-assessment at each visit, in the form of a structured questionnaire in which patients were asked to score each variable as worse, no change, or improved after the therapy, as compared to the time before treatment was started. All patients were followed up to evaluate the efficacy of therapy at one, two, four, and twelve weeks after treatment. Tolerability to treatment was also assessed by using a three-point scale as follows: very good (no signs and symptoms); moderate (transient side-effects); and poor (adverse events which resulted in discontinuation of therapy).

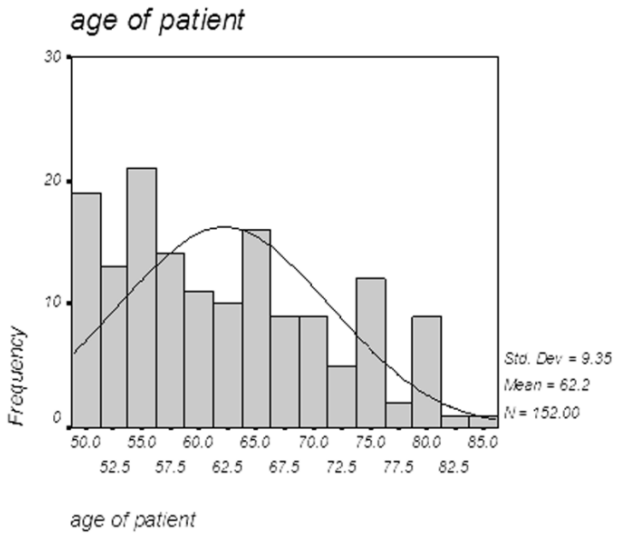
Statistical analysis

Statistical analysis of the results was performed with the SPSS (Ver15for Windows) with the two-tailed t-test, and Chi-Square test. In this analysis a p value of < 0.05 was considered significant.

Results

A total of 152 patients participated in the study, 76 of whom were included in Group 1 (patients with a rash with a duration of less than 72 hours) and 76 of whom were included in Group 2 (patients with a rash with a duration of more than 72 hours).

Figure 1. The distribution of age at onset of herpes zoster



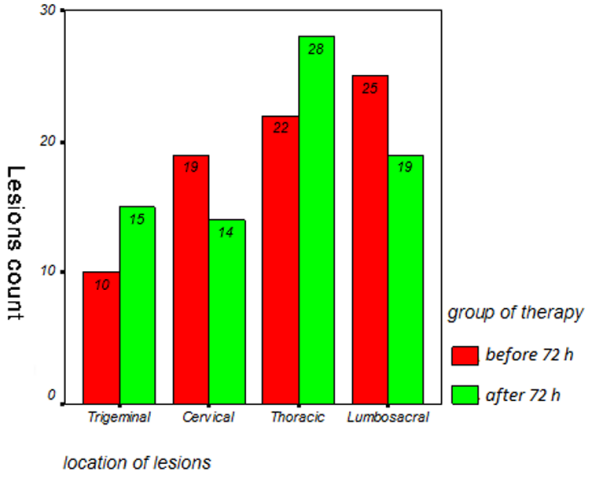
Demographic characteristics

Of the 152 participants, the youngest was 50 years old and the oldest one was 85; the mean age was 62.2 (SD ± 9.3) (Figure 1). There were no significant differences between Group 1 and Group 2 regarding age, gender, and clinical presentation.

Dermatomes differences

The thoracic area was the most common location of the herpes zoster lesions (n = 50; 32.9%), followed by the lumbosacral (n = 44; 28.9%), cervical (n = 33; 21.7%), and trigeminal (n = 25, 16.4%) areas (Figure 2). There were no significant differences in mean scores of dermatomes involvement among the patients (p = 0.348).

Figure 2. Dermatomal distribution of herpes zoster lesions



Duration of lesions healing

Skin lesions rapidly healed and complete re-epithelialization occurred in 7 to 10 days in Group 1 and 12 to 25 days in Group 2.

Acute zoster-associated pain

The mean verbal rating scale scores were 3.77 ± 0.6 versus 3.67 ± 0.44 (p = 0.73) in Group 1 and Group2, respectively. Reduction in initial pain intensity (PPR) at Day 7 was obtained in 129 patients including 65patients (85.5%) in Group 1 and 64 patients (84.2%) in Group 2. No significant difference between the two groups was evident (p = .821). On Day 7, almost 14.5% of Group 1 patients reported interference with sleep, as compared to 15.8% of Group 2 patients (NPR).

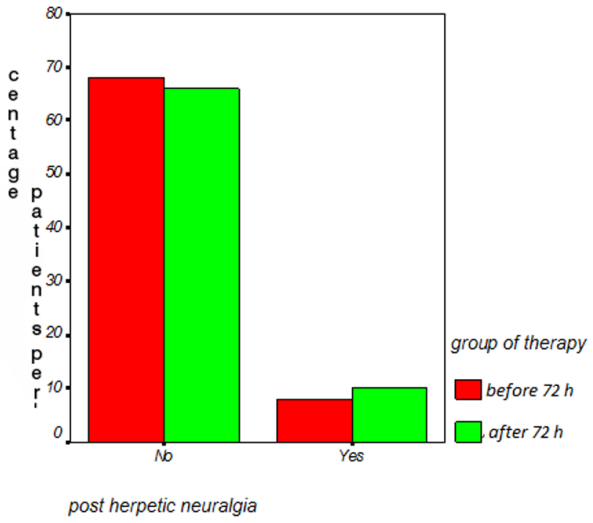
A further reduction in initial pain intensity (PPR) at Day 14 was obtained in 134 patients, 68 (89.5%)

of whom were from Group1 and 66 (86.8%) of whom were from Group 2. On Day 14, almost 13.2% of the patients in Group 2 had pain as compared with 10.6% of those in Group 1(NPR). No significant difference between the two groups was evident (p = .616).

By the fourth week, 134 patients (88.2%) had absent or mild pain (CPR); 68 of these patients (89.5%) were from Group1 and 66 (86.8%) were from Group 2. On Day 28, almost 13.2% of the patients in Group 2 had pain as compared to 10.6% of the patients in Group 1. Again, no significant difference between the two groups was evident (p = .616).

By the fourth week, the failure rate of our study (*i.e.*, the patients who developed PHN), was 18 patients (11.8%) (Figure 3). Among these 18 patients, nine had lumbosacral lesions, six had thoracic lesions, and three had trigeminal lesions. The incidence of PHN in male was higher than in female subjects, with 14 affected men (77.7%) compared to four affected women (22.3%).

Figure 3. Percentage of patients who developed P.H.N by week 4.



By the 12th week of patient follow-up, just six patients had PHN. At the end of study period, 146 patients (96%) graded their pain as mild to no discomfort (CPR), and just six patients (4%) still had severe intractable pain (NPR).

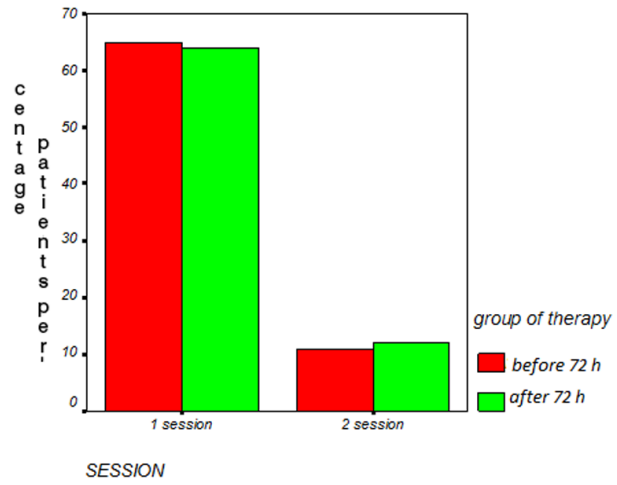
The results of VRS in Groups 1 and2 at the beginning of the study and after the first, second, fourth, and 16th weeks after treatment are shown in Table 1.

The mean VRS score was not different between the two groups (3.77 ± 0.6 versus 3.67 ± 0. 0.44; p = 0.73 in Groups 1 and 2 respectively) after four weeks. The mean VRS score changed significantly in both groups over the duration of the study (p = 0.001), but there was no difference between two groups (0.88 ± 0.66 for Group 1 versus 0.94 ± 0.72 for Group 2; p = 0.66). Furthermore, after three months, there was no difference between the treatment results in the two groups (0.51 ± 0.13 versus .0.54 ± 0.19; p = 0.77 for Group 1 and Group 2 respectively).

Sessions of treatment

In the first session of treatment, 118 patients (91.5%) achieved PPR. Following the treatment, 16 patients (6.96%) achieved a further PPR in two different sessions. There was a significant difference in patient response to treatment in the two sessions of treatment in comparison to the first session (p =.003) (Figure 4).

Figure 4. Percentage of complete pain response in first and second treatment sessions.



Tolerance

The overall treatment was well tolerated in most patients. None of the patients stopped treatment because of adverse effects of acyclovir. Tolerability of acyclovir was considered “very good” in 142 cases (93%), and “moderate” in 10 cases (7%). Six patients suffered from nausea and vomiting, five patients had fatigue, three patients developed skin rashes, and reversible BUN increase was detected in three patients.

Table 1. The patients' post-herpetic pain results after first, second, fourth and twelfth week and one year after therapy

	Group 1 (n = 76)	**Group 2 (n = 76)**	**p Value**
Mean VRS at beginning of study	3.77 ± 0.6	3.67 ± 0.44	(p = 0.73) NS
Mean VRS after first week	2.19 ± 1.21	2.23 ± 1.19	(p = 0.76) NS
PPR(%) after first week	65 (85.5%)	64 (84.2%)	(p = 0.821) NS
Mean VRS second week	2.10 ±1.11	2.12 ± 1.07	(p = 0.88) NS
PPR (%) second week	68 (89.5%)	66 (86.6%)	(p = 0.61) NS
Mean VRS first month	0.88 ± 0.66	0.94 ± 0.72	(p = 0.66) NS
CPR after first month	68 (89.5%)	66 (86.6%)	(p = 0.61) NS
Mean VRS third month	0.51 ± 0.13	0.54 ± 0.19	(p = 0.77) NS
CPR after third month	74 (97.3%)	72 (94.7%)	(p = 0.73) NS
Mean VRS twelfth month	0.32 ± 0.12	0.39 ± 0.14	(p = 0.88) NS
CPR after twelfth month	75 (98.6%)	74 (97.3%)	(p = 0.89) NS

VRS: Verbal Rating Scale (0-4)
CPR: Complete Pain Response
PPR: Partial Pain Response
NS: Not statistically significant (p > 0.05)

Discussion

Herpes zoster is painful by itself and is sometimes followed by neuralgia. Post-herpetic neuralgia, defined as debilitating pain, persists beyond four weeks of rash onset. The risk of developing post-herpetic neuralgia rises with age, which influences both duration and severity of the neuralgia [15]. It may affect up to one half of patients over 50, and is very common after trigeminal nerve zoster [2].

In some studies, the best predictor of persistent pain after herpes zoster was the presence of severe prodromal pain or severe pain at presentation and old age [16-20]. Female gender and cranial or sacral locations were additional risk factors for persistent pain in one of these studies [20].

Oral acyclovir (800 mg, administered orally five times a day for seven to ten days) has been shown to accelerate the rate of coetaneous healing of herpes zoster lesions and reduce the severity of acute pain [6,10-12,21-23]. In a reanalysis of the largest US placebo-controlled trial, the median duration of zoster-associated pain in acyclovir recipients was 20 days, compared to 62 days for placebo recipients [24]. Early clinical trials have suggested that acyclovir has no benefit in reducing the duration of PHN [6,21,25] but more recent information supports the contrary. A meta-analysis of five clinical trials suggests that beginning oral administration of acyclovir within 72 hours of rash onset may reduce the incidence of residual pain within six months by 46% in immunocompetent adults [26]. However, no study has indicated that antiviral therapy is not beneficial if it is started after 72 hours of rash onset. Wood *et al*. compared acyclovir administration for seven days to acyclovir administration for 21days, with and without prednisolone consumption, in the treatment of acute herpes zoster [27]. They found that treatment with acyclovir for 21 days, compared to seven days or the addition of prednisolone, did not reduce the frequency, duration or severity of PHN [27]. The findings of the present study add to this information that administration of acyclovir after the third day of the appearance of herpetic rash is just as effective in the treatment of post-herpetic neuralgia compared to early treatment (before 72 hours) with this agent.

In our study, a significant improvement in pain intensity was evident by the seventh day of treatment in the majority of patients. Within two weeks of therapy, an excellent PPR was observed in 68 patients of Group 1 (89.5%) and 66 patients of Group 2 (86.8%).

We showed that short-course oral acyclovir (800 mg five times a day for four days), even if started within the first 21 days of zoster rash, was capable of shortening the healing time and alleviating the severity acute zoster pain as well as preventing PHN. Acyclovir proved to be successful within the first two weeks of treatment, providing remarkable improvement in acute zoster pain. All sites (trigeminal, cervical, thoracic, lumbosacral) showed

an equal response. In the present study similar daily doses (800 mg five times a day) administered for a short period of time (just for 4 days), cured 146 cases (96%) of acute herpes zoster pain (CPR). An early clinical response to acyclovir was observed in most patients of this study, even in those who received the drug after 72 hours of rash. We did not observe a significant difference in therapeutic responses with respect to rash duration. Seventy-six of the 152 patients had suffered from the disease for a relatively short period of time (three days or less). The remaining76 cases had suffered from the disease for a longer period (4-21 days). Our study proved the efficacy of therapy which starts even after 72 hours of herpes zoster infection. Hence we think that the presence and activity of varicella-zoster virus beyond 72 hours has a possible role in the persistence of acute herpes zoster pain and PHN.

Another potential advantage of our therapy was the efficacy of short-course (four days) therapy in decreasing acute herpes zoster pain and preventing PHN.

Based on these results, we propose that short-course oral acyclovir (a four-day treatment) can be offered as an alternative to the 7-to 10-day therapy, particularly in an outpatient setting. To the best of our knowledge, no other study has compared the efficacy of acyclovir before and after the first 72 hours of herpes zoster onset.

Complete pain response was achieved after a mean of four weeks in both groups. Two sessions of treatments with acyclovir could not yield better results than a single treatment session. Our results also showed significantly lower rates of PHN compared with those reported in previously published data. Only six subjects in our study experienced PHN by the end of three months. Pain intensity reduction on Day 7 versus Days 14 and 28 was significantly higher. The reason for this observation is unclear, but we think that the activity and living mass of the virus is one of the important causes of pain in HZ patients and more reduction in the mass of the living virus on the seventh day could be responsible for the higher pain reduction rating. While optimal therapy for herpes zoster is desired, safety aspects must be taken into account, and shorter courses of acyclovir therapy appear to result in fewer adverse effects than longer courses.

Limitations

This investigation has some limitations. First, due to the time-based evaluation of response to treatment, a double-blinded study was not possible. Additionally, the limited population under examination undermines a definitive conclusion that short-course acyclovir in all patients and in all populations can be safe and effective. Further proliferated studies with a larger number of patients are needed before the conclusion that this therapeutic method is completely effective in all HZ patients can be reached.

Conclusion

The results of this study show that short-course oral acyclovir (800 mg five times a day for four days) is capable of shortening the healing time and ending acute zoster pain, as well as preventing the occurrence of PHN, even if started within the first 21 days of onset of zoster rash. These findings will be useful for physicians using this treatment protocol in treating HZ patients older than 50 years for prevention and treatment of PHN.

References

1. Wood MJ (1986) Herpes zoster in immunocompetent patients. Res Clin Forums 8: 61-68.
2. Brantley JS, Hicks L, Sra K, Tyring SK (2006) Valacyclovir for the treatment of genital herpes. Expert Rev Anti Infect Ther 4: 367-376.
3. Weinberg JM and Scheinfeld NS (2003) Cutaneous infections in the elderly: diagnosis and management. Dermatol Ther 16: 195-205.
4. Wang SM (2007) An integrative approach for treating post-herpetic neuralgia--a case report. Pain Pract 7: 274-278.
5. Quan D, Hammack BN, Kittelson J, Gilden DH (2006) Improvement of post-herpetic neuralgia after treatment with intravenous acyclovir followed by oral valacyclovir. Arch Neurol 63: 940-942.
6. Vujacich C, Poggi E, Cecchini D, Luchetti P, Stamboulian D (2008) Clinical and epidemiological aspects of herpes zoster. Medicina (B Aires) 68: 125-128.
7. Wagstaff AJ, Faulds D, Goa KL (1994) Acyclovir: A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 47: 153-205.
8. Asano-Mori Y, Kanda Y, Oshima K, Kako S, Shinohara A, Nakasone H, Sato, H., Watanabe, T., Hosoya, N, Izutsu, K, Asai, T, Hangaishi, A, Motokura, T, Chiba, S, Kurokawa, M (2008) Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. Am J Hematol 83:472-476.
9. Sra KK and Tyring SK (2004) Treatment of post-herpetic neuralgia. Skin Therapy Lett 9: 1-4.
10. Wood MJ, Ogan PH, Mckendrick MW, Care CD, McGill JI, Webb EM (1988) Efficacy of oral acyclovir treatment of acute herpes zoster. Am J Med 85:79-83.
11. Huff JC, Bean B, Balfour HH Jr, Laskin OL, Connor JD, Corey L, Bryson YJ, McGuirt, P (1988) Therapy of herpes zoster with oral acyclovir. Am J Med 85: 84-88.
12. Volpi A, Gross G, Hercogova J, Johnson RW (2005) Current management of herpes zoster: the European view. Am J Clin Dermatol 6: 317-325.

13. Pavan-Langston D (2008) Herpes zoster antivirals and pain management. Ophthalmology 115 Suppl2: 13-20.
14. Gracely RH (1992) Evaluation of multi-dimensional pain scales. Pain 48: 297-300.
15. Portenoy RK, Duma C, Foley KM (1986) Acute herpetic and postherpetic neuralgia: clinical review and current management. Ann Neurol 20: 651-664.
16. Opstelten W, Eekhof J, Neven AK, Verheij T (2008) Treatment of herpes zoster. Can Fam Physician 54: 373-377.
17. Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Platt R (1997) Risk factors for post-herpetic neuralgia. Arch Intern Med 157: 1217-1224.
18. Whitley R, Shukla S, Crooks R (1998) The identification of risk factors associated with persistent pain following herpes zoster. J Infect Dis 178: 71-75.
19. Decroix J, Partsch H, Gonzalez R, Mobacken ., Goh C, Walsh J, Shukla S, Naisbett B and on behalf of the Valaciclovir International Zoster Assessment Group (VIZA) (2000) Factors influencing pain outcomes in herpes zoster: an observational study with valaciclover:. Eur Acad Dermatol Venereol 14: 23-33.
20. Meister W, Neiss A, Gross G, Doerr, H., Höbel, W, Malin J, von Essen J, Reimann B, Witke C, Wutzler P (1998) A prognostic score for post-herpetic neuralgia in ambulatory patients Infection. 26: 359-363.
21. Peterslund NA, Seyer-Hansen K, Ipsen J, Esmann V, Schonheyder H, Juhl H (1981) Acyclovir in herpes zoster. Lancet 2: 827-830.
22. Madkan VK, Arora A, Babb-Tarbox M, Aboutlabeti S, Tyring S (2007)Open-label study of valacyclovir 1.5 g twice daily for the treatment of uncomplicated herpes zoster in immunocompetent patients 18 years of age or older. J Cutan Med Surg 11: 89-98.
23. Niv D and Maltsman Tseikhin A (2005) Post-herpetic neuralgia: the never-ending challenge. Pain Pract 5: 327-40.
24. Huff JC, Drucker JL, Clemmer A, Laskin OL, Connor JD, Bryson YL, Balfour HH (1993) Effect of oral acyclovir on pain resolution in herpes zoster: a re-analysis. J Med Virol 1 Suppl: 93-96.
25. Van den Broek PJ, Van der Meer JW, Mulder JD, Versteeg J, Mattie H (1984) Limited value to acyclovir in the treatment of uncomplicated herpes zoster: a placebo-controlled study. Infection 12: 338-341.
26. Jackson JL, Gibbons R, Meyer G, Inouye L (1997) The effect of treating herpes zoster with oral acyclovir in preventing post-herpetic neuralgia: A meta-analysis. Arch Intern Med 157: 909-912.
27. Wood MJ, Johnson RW, McKendrick MW, Taylor J, Mandal BK, Crooks J (1994) A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. N Eng J Med 330: 896-900.

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