HERPES ZOSTER – ROLE OF SINGLE DOSE OF GABAPENTIN WITH ACYCLOVIR THERAPY IN REDUCTION OF ACUTE PAIN AND PREVENTION OF POSTHERPETIC NEURALGIA

Shathruvedula Ravindra Nath[1]

[1]*Assistant Professor (Incharge Professor), Department of Dermatology, Mahatma Gandhi Memorial Hospital, Warangal, Telangana, India.*

ABSTRACT

AIMS

To evaluate the role of single dose of gabapentin 900 mg in combination with acyclovir therapy in reduction of acute pain and prevention of postherpetic neuralgia in herpes zoster.

METHODS

25 patients were designated as a study group and were given acyclovir therapy 800 mg 5 times daily for 7 days along with single dose of gabapentin 900 mg on the first day of the therapy.

10 patients were kept as a control group and were given acyclovir therapy alone 800 mg 5 times daily for 7 days. Results with reference to reduction of acute pain and development of postherpetic neuralgia were recorded and analysed.

RESULTS

Two patients in study group reported 'excellent' relief of pain, 20 patients reported 'good pain' relief, 2 patients reported 'moderate' pain relief, and 1 patient reported 'poor' pain relief. 2 patients developed postherpetic neuralgia. In control group, 1 patient reported 'good' pain relief. 5 patients reported 'moderate' pain relief. 4 patients reported 'poor' relief of pain. 4 patients developed postherpetic neuralgia.

CONCLUSION

Gabapentin 900 mg single dose in combination with acyclovir therapy 800 mg 5 times daily for 7 days plays a significant role in reduction of acute pain and prevention of postherpetic neuralgia in herpes zoster. A larger study in patients with risk factors for postherpetic neuralgia is required in this regard.

KEYWORDS

Herpes zoster, Acute Pain, Acyclovir, Postherpetic Neuralgia, Single Dose Gabapentin.

HOW TO CITE THIS ARTICLE: Nath SR. Herpes zoster – role of single dose of gabapentin with acyclovir therapy in reduction of acute pain and prevention of postherpetic neuralgia. J. Evid. Based Med. Healthc. 2016; 3(35), 1721-1727.

DOI: 10.18410/jebmh/2016/384

INTRODUCTION: Herpes zoster or shingles is the painful eruption of rash caused by Varicella zoster virus generally unilateral. The virus persists silently in the dorsal root ganglia of an individual who had an attack of chicken pox. Later it reactivates from its dormant state in about 25% of people and travels along the sensory nerve fibres to produce vesicular lesions in the dermatome supplied by that nerve.[1] Cellular immunity generally prevents the clinical expression of Varicella zoster virus by an unknown mechanism.[2] The decrease of cellular immunity to the virus with increasing age or immunocompromised state is associated with clinical re-activation.[2]

The eruption most commonly manifests in individuals of around 60 years of age. Studies have revealed that with each increasing decade of life, the incidence of Varicella steadily increases amounting for a lifetime risk of developing herpes zoster for approximately one in every two people.[3] Apart from increasing age, the other major risk factor is immunosuppression which increases the risk of developing severe and frequent herpes zoster.[4,5] Herpes Zoster is one of the earliest opportunistic infections observed in patients with HIV as their CD4, T cell count starts declining.[6]

The pain associated with herpes zoster can be debilitating with a serious impact on the quality of life.

The pain associated with acute zoster and postherpetic neuralgia is neuropathic and results from injury of the peripheral nerves and altered central nervous system signal processing.[7]

The role of antiviral therapy in reduction of acute neuropathic pain is well known, but its role in postherpetic neuralgia has been limited as shown by many clinical studies.[8] Steroid therapy frequently used as adjunct to antiviral therapy in herpes zoster has also shown to have little or no effect on postherpetic neuralgia.[9]

The addition of oral prednisolone to acyclovir treatment has been shown to reduce pain, accelerate healing of the lesions and allow a faster return to daily activities.[10]

Similarly, a single dose of epidural methylprednisolone in combination with a local anaesthetic is a useful additive

Financial or Other, Competing Interest: None.
Submission 28-03-2016, Peer Review 13-04-2016,
Acceptance 22-04-2016, Published 30-04-2016.
Corresponding Author:
Dr. Shathruvedula Ravindra Nath,
H. No. 11-24-57, Road No. 3, M. V. Colony,
Desaipet Road, Warangal-506002.
E-mail: drsravindranath009@gmail.com
DOI: 10.18410/jebmh/2016/384

treatment in resolving the acute pain, but has no impact on development of postherpetic neuralgia.[11]

There has been wide usage of tricyclic antidepressants in the management of chronic neuropathic conditions, but their impact on reduction of acute pain was not evaluated but a prevalence in reduction of postherpetic neuralgia at 6 months was reported.[12]

A randomised controlled trial by Berry and Peterson has shown that single dose of 900 mg of anticonvulsant gabapentin reduces acute pain in herpes zoster.[13]

The present study is aimed at evaluating the role of single dose of 900 mg of gabapentin in combination with acyclovir therapy 800 mg 5 times daily for 7 days in reduction of acute pain in herpes zoster and prevention of postherpetic neuralgia.

METHODS: The study was conducted in Department of Dermatology, Mahatma Gandhi Memorial Hospital, Warangal over a period of 1 year and is approved by local research Ethical Committee. A detailed clinical history was recorded with regard to age, sex, site of onset of lesion, mode of onset of lesion, duration of lesions, evolution of lesions, and type of pain, etc.,

The diagnosis of herpes zoster was based on clinical features consisting of sudden onset of groups of vesicles arranged in dermatomal pattern associated with erythema, pain and burning sensation. Viral culture, a direct immunofluorescence assay and polymerase chain reaction techniques were not done as these facilities were not available in our institute.

In all cases, a routine haematology and other laboratory investigations were done. Chest x-rays were taken whenever necessary. Children below 10 years, patients with more than 100 hours of duration after the onset of rash at that time of reporting and patients with prior antiviral therapy were excluded. All the 25 patients of study group were given acyclovir therapy 800 mg 5 times daily for 7 days with a single dose of gabapentin on the first day of starting antiviral therapy. 10 patients were kept as a control group and were given acyclovir therapy alone for 7 days. NSAIDS were not given to any of these patients to avoid masking effect of NSAIDS on role of gabapentin in reduction of acute pain. All the patients belonging to study group and control group were followed at the intervals of 7 days, 14 days, 1 month, 3 months and 5 months interval regarding the healing of the lesions, resolution or persistence of acute pain and onset of postherpetic neuralgia and findings were recorded accordingly. In terms of perception of pain, the patients were kept on a visual analogue scale ranging from 0-10 (0=no pain, 10=maximum pain felt). Only pain characteristics of control group patients were recorded. Other clinical details were not much stressed.

No pain	- Score 0.
Mild pain	- Score 1–3.
Moderate pain	- score 3-6.
Severe pain	- Score 6-10.

Post therapy, the patients' relief of pain was recorded in terms of pain relief reported by the patients in the following terminology. 1) No relief. 2) Poor relief. 3) Moderate relief. 4) Good relief. 5) Excellent relief.

RESULTS: There were 25 patients in the present study with 20 males and 5 females. 10 patients who were kept as control group consisted of 8 males and 2 females (The control group was given acyclovir therapy only). The youngest patient was 14 years male and the oldest patient was 70 years old female. No history of an earlier attack of Varicella could be elicited from any of these patients. There were 6 patients in 15 to 20 years' age group, 2 patients in 20 to 30 years' age group 6 patients in 30 to 40 years' age group, 8 patients in 40–50 years' age group, 1 patient in 50-60 years' age group and 2 patients in 60 to 70 years' age group. Majority of patients were found to be 40 to 50 years' age group. (Table no 1.)

	Male	**Female**	**Total**
15 to 20 years	6	0	6
20 to 30 years	2	0	2
30 to 40 years	4	2	6
40 to 50 years	6	2	8
50 to 60 years	1	0	1
60 to 70 years	1	1	2
	20	**5**	**25**
Table 1			

In 19 patients, the dermatomes involved are thoracic (76%), followed by cervical 2 patients (8%), followed by trigeminal 2 patients (8%), and lumbosacral 2 patients (8%) (Table 2)

	Male	**Female**	**Total**
Thoracic	15	4	19
Trigeminal	2	0	2
Cervical	2	0	2
Lumbar	1	1	2
Total	**20**	**5**	**25**
Table 2			

Rash: There were 22 patients present with profuse rash with groups of vesicles arranged in dermatomal pattern. Only 3 patients presented with fewer discrete vesicular lesions though arranged in dermatomal pattern. (Table no. 3).

	Female	**Male**	**Total**
Discrete	1	2	3
Profuse	4	18	22
Vesicles	5	20	25
Crust	0	0	0
Table 3			

In 23 patients, duration of reporting to the hospital after onset of the rash ranged from 48–72 hours.

Only 2 patients reported within 24 hours after the onset of the rash.

Pain: In the study group 8 Patients complained of intense pain of spasmodic shooting type. All these patients were above 40 years of age. There were 15 patients with moderately intense pain of burning and tingling type. Only 2 patients below 20 years of age presented with mild pain. (Table No. 4.)

	Male	Female	Total
No pain	0	0	0
Mild	2	0	2
Moderate	14	1	15
Intense	4	4	8

Table 4: Pain Study Group

In the control group, among the total 10 patients, 2 patients complained of mild pain and 7 male and one female patient complained of moderate pain, No patient complained of severe pain. (Table No. 5).

	Male	Female	Total
No pain	0	0	0
Mild	2	0	0
Moderate	7	1	8
Intense	0	0	0

Table 5: Pain - Control Group

These patients were kept on visual analogue scale ranging from 0–10 (0=no pain) (10=Maximum pain felt ever in life.)

In the study group, there were 2 patients with VAS score of 2 , 5 patients with VAS score of 4, 10 patients (9 male and 1 female) with VAS score of 5, and 8 patients (4 male and 4 female) with VAS score of 8. (Table No. 6)

	Male	Female	Total
1	0	0	0
2	2	0	2
3	0	0	0
4	5	0	5
5	9	1	10
6	0	0	0
7	0	0	0
8	4	4	8
9	0	0	0
10	0	0	0

Table 6: Pain-Visual Analogue Score Study Group

In the control group, there were 2 patients with VAS score of 3 and 8 patients (7 male and 1 female) with VAS score of 5. (Table No. 7)

	Male	Female	Total
1	0	0	0
2	0	0	0
3	2	0	2
4	0	0	0
5	7	1	8
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0

Table 7: Pain-Control Group Visual analogue Score

Post therapy in the study group, 1 male patient reported poor relief of pain, 2 male patients reported moderate pain relief and 20 patients (15 male and 5 female) reported good relief. 2 young male patients below 20 years age reported excellent relief. 2 male patients in study group reported with post herpetic neuralgia. In the control group, 3 male patients reported poor relief. 1 patient reported 'good' pain relief and 6 patients (5 male 1 female) reported moderate pain relief. In control group, 4 patients reported with post herpetic neuralgia. (Table No. 8)

	Study group			Control group		
	Male	Female	Total	Male	Female	Total
No relief	0	0	0	0	0	0
Poor relief	1	0	1	3	0	3
Moderate relief	2	0	2	5	1	6
Good relief	15	5	20	1	0	1
Excellent relief	2	0	2	0	0	0
Post herpetic neuralgia	2	0	2	4	0	4

Table 8: Post Therapy Pain Relief

DISCUSSION: Pain in the most common symptoms of herpes zoster infection often preceding eruption by days to weeks[14,15] and occasionally is the only manifestation. Most patients developed deep aching or burning pain, altered sensation to touch, (paraesthesia) that may be painful (dysaesthesia) or exaggerated response to stimuli (hyperaesthesia) or electric shock like pain.[16]

The pain of zoster tends to undergo spontaneous resolution with time.[17] In the past, the pain resulting from herpes zoster was arbitrarily differentiated from postherpetic neuralgia although the nature and timing of symptoms often overlap.[2]

The most common definition of postherpetic neuralgia is presence of pain for more than one month in duration after the onset of eruption of zoster.[18,19] The condition has also been defined as pain persisting after the crusting of lesions, after 6 weeks or after 6 months.[20]

Recently, the term zoster associated pain has been used to describe all pain that occurs after the onset of rash.[21] Nearly all patients have pain associated with acute herpes zoster and 10 to 70% have postherpetic neuralgia.[22,23]

After the injury, the peripheral neurons discharge spontaneously, have lower action thresholds and display exaggerated response to stimuli.[2] Axonal regrowth after the injury produces nerve sprouts that are also prone to unprovoked discharge.[24] The excessive peripheral activity is thought to lead to hyper excitability of the dorsal horn

resulting in exaggerated central nervous system response to all output.[24,25] These wide array of changes may be so complex that it will be difficult for any single therapeutic approach to ameliorate all the abnormalities. Studies have suggested that if given within a period of 72 hours of appearance of the rash in herpes zoster, the antiviral drugs acyclovir or famciclovir or valaciclovir will reduce acute pain in immunocompetent person with herpes zoster.[26,27,28]

Placebo controlled trials have revealed that acyclovir 800 mg given five times daily shortened the duration of viral shedding, halted the formation of new lesions more quickly, hastened the rate of healing and decreased severity of acute pain.[29,30] With regard to duration and frequency of postherpetic neuralgia variable benefits were reported. Acyclovir was found to be significantly superior to placebo in decreasing the duration of zoster associated pain defined as continuum of pain measured from onset until final resolution.[31]

Some models devised to explain the pathogenesis of postherpetic neuralgia suggest that early attenuation of acute pain may prevent the initiation of central mechanism of chronic pain thereby lowering the risk of postherpetic neuralgia.[32]

The above findings are a useful pointer to the rationale of using a combination of acyclovir and single dose of 900 mg gabapentin which may attenuate acute pain in the present study.

Gabapentin is an anticonvulsant drug that was primarily developed and approved as an adjunct therapy for treatment of partial seizures in both adults and paediatric population.[33] Gabapentin is the structural analogue of gamma amino butyric acid (GABA) but does not act by binding to GABA α and GABA β, but it binds to alpha 2 delta site of voltage dependent calcium channels thereby modulating the influx of calcium which results in reduction of excitatory neurotransmitter release.[34]

A decrease in excitatory transmitter leads to decreased alpha amino–3 hydroxy-5 methylisoxazole-4 propionic acid (AMPA) and glutamate receptor activation and a decrease in pain transmission signalling.[35]

Gabapentin, when given at least three times per day, is effective in decreasing postherpetic neuralgia.[33] This is due to pharmacokinetics of the drug which show peak plasma level achieved at 2-3 hours after oral administration.[36]

Gabapentin 900 mg single dose when given in combination with acyclovir may attenuate acute pain (acyclovir by reducing viral load and hastening the healing of lesion there by preventing further neuronal damage, and gabapentin by reducing the excitatory neurotransmitter release).

Thus, both drugs acting synergistically (though by different nodes of action) in combination in attenuating acute neuronal pain thereby playing a significant role towards reduction of acute pain and prevention of postherpetic neuralgia. The risk factors for postherpetic neuralgia include greater severity of rash, prodrome and severe pain during the acute phase.[37]

In the present study, there were 25 patients of different age groups, maximum number of patients being present in the age group of 40-50 years. There was only one patient in 50–60 years age group. The male and female ratio was 4: 1. No comment can be made on sex ratio based on the small size of the study. Maximum number of patients are seen in thoracic group followed by trigeminal, cervical and lumbosacral group.

In the present study, two young patients complained of mild pain with VAS of 2 and after therapy with acyclovir and gabapentin 900 mg single dose, the rash healed completely and there was excellent (100%) pain relief. They did not report any postherpetic neuralgia in a followup period of 3 and 5 months interval.

Another group complained of VAS score of 4(30%) and 5(70%). This group consisted of 60% of the total patients and majority of the patients were 20 to 50 years age group. Following combination therapy with acyclovir and single dose gabapentin 900 mg, all the patients reported "good" pain relief with complete resolution of zoster rash with residual post inflammatory pigmentation.

Another group which consisted of 32% of total patients complained of severe pain at onset with VAS score of 8, all these patients were in the age of 40 to 65 years and one female patient was 70 years old. These patients displayed risk factors for development of postherpetic neuralgia. All except one showed good pain relief following therapy. One 45-year-old male patient reported for treatment after 72 hours of onset of rash. He developed secondary bacterial infection of the rash. He complained of poor relief of pain even after 1 week of acyclovir therapy and therapy was extended for a total period of 10 days. It is not known whether delay in reporting late at the hospital or secondary bacterial infection was the cause of poor pain relief.

Among the herpes zoster patients who are below 50 years of age as many as 10–20% will develop postherpetic neuralgia.[38] In the present study, 8% of patients reported with postherpetic neuralgia. Among these two patients, one reported of moderate pain relief whereas the other reported of poor pain relief. This patient had secondary bacterial infection and he reported late to the hospital also.

Among the 5 female patients in the present study, 3 patients had risk factors for postherpetic neuralgia i.e. female sex, age around 50 years and severe pain with VAS score of 8 but all of these patients reported good pain relief and did not report any postherpetic neuralgia on a followup period of 3 and 5 months interval.

In the control group, among the 10 patients, 6 patients (60%) reported moderate pain relief, 1(10%) patient reported with good pain relief and 3 patients (30%) reported with poor pain relief and these 4 patients developed postherpetic neuralgia and all these patients were below 40 years of age.

Gabapentin has long been considered a first line agent in the treatment of postherpetic neuralgia. Majority of the pathological events that lead to neuropathic pain and postherpetic neuralgia may have occurred by the time rash appears.[39] Administration of a suitable voltage dependent

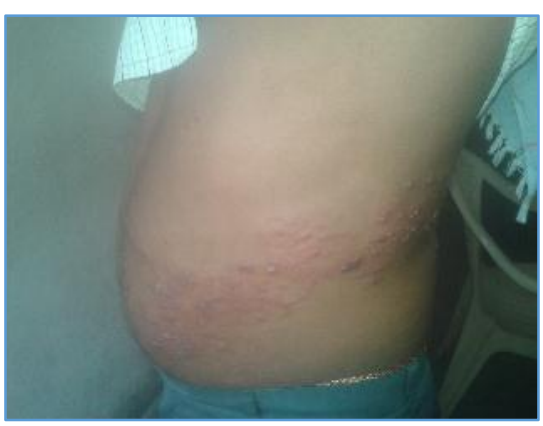
calcium channel modulator like gabapentin may provide an opportunity to intervene while some of the changes are still reversible. There is a decrease in absolute bioavailability of gabapentin from 60 to 33% as the dose increased from 900 to 3600 mg/day,[32] a fact which indicates that higher dose of gabapentin does not have much advantage over the lower dose. Moreover gabapentin has dose limiting side effects, the most common include somnolence (27.4%), dizziness (23.9%) and ataxia (7.1%).[40]

Though majority of the patients in the present study did not have risk factors for the development of postherpetic neuralgia, the findings revealed that a combination of acyclovir therapy with single dose of gabapentin 900 mg on the first day of starting of therapy plays a significant role in reduction of acute pain and also some pivotal role in prevention of postherpetic neuralgia as evidently seen from findings of control group where in 40% reported postherpetic neuralgia whereas only 8% of the study group reported postherpetic neuralgia.

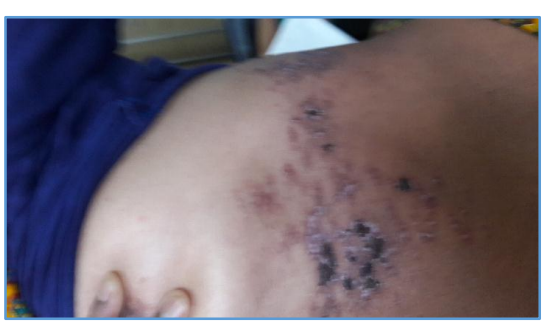
A randomised controlled trial by Berry and Peterson has shown that single dose of 900 mg of anticonvulsant gabapentin reduces acute pain in herpes zoster.[13]

CONCLUSION: From the present study, it may be conclusively said that gabapentin single dose in combination with acyclovir therapy plays a vital role in reduction of acute pain and prevention of postherpetic neuralgia. A larger study with patients having risk factors for postherpetic neuralgia is required to further evaluate the findings of the present study.

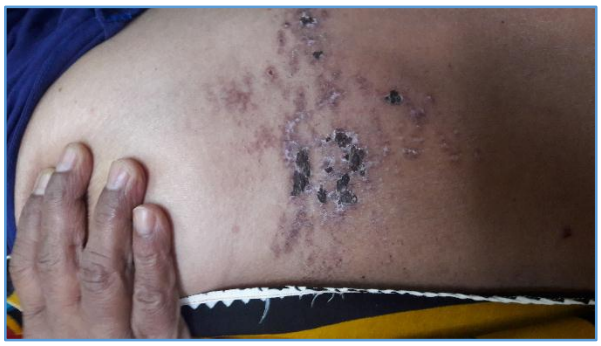
A patient with healed herpic zoster lesion:



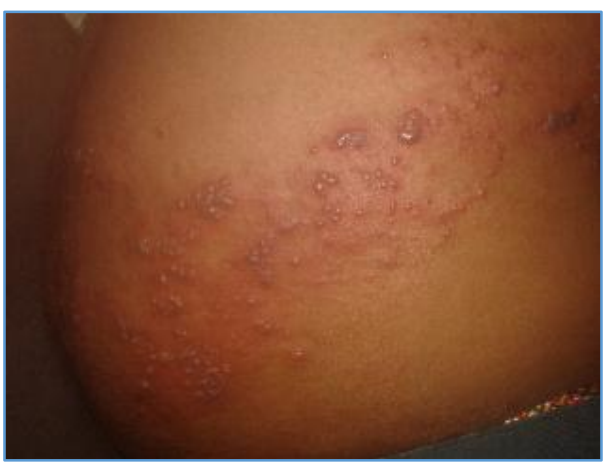
A PATIENT WITH HERPIC ZOSTER PHOTO 1



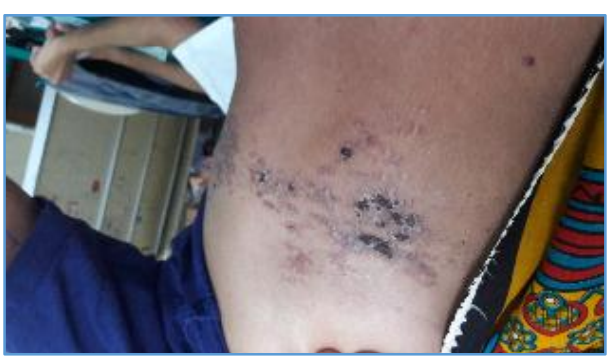
A PATIENT WITH HEALED HERPIC ZOSTER LESION PHOTO 1



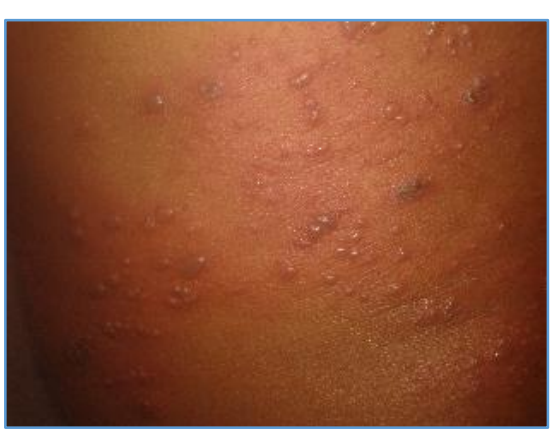
A PATIENT WITH HEALED HERPIC ZOSTER LESION PHOTO 2



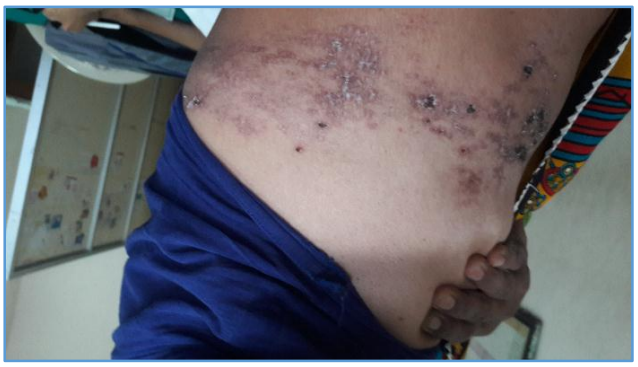
A PATIENT WITH HERPIC ZOSTER PHOTO 2



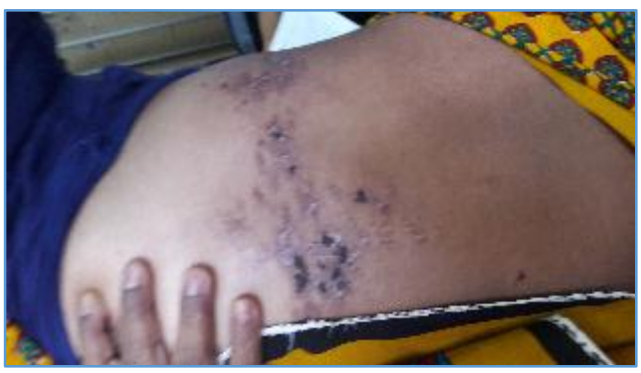
A PATIENT WITH HEALED HERPIC ZOSTER LESION PHOTO 3



A PATIENT WITH HERPIC ZOSTER PHOTO 3



A PATIENT WITH HEALED HERPIC ZOSTER LESION PHOTO 3



A PATIENT WITH HEALED HERPIC ZOSTER LESION PHOTO 2

REFERENCES:

1. David W Warenharm, Judith Breuer. Herpes zoster. British Medical Journal 2007;334(7605):1211-1215.
2. Rhonda G Kost, Stephen E Starus. Postherpetic neuralgia pathogenesis treatment and prevention. The New England Journal of Medicine 1996;335(1):32-41.
3. Insinga RP, Itzler RF, Pelissier JM, et al. The incidence of herpes zoster in a United States administrative data base. J Gen inter Med 2005;20(8):748–753.
4. Gnann JW, Whitley RJ. Natural history and treatment of varicella–zoster in high risk populations. J Hosp infet 1991;18(Supple A):317-329.
5. Gnan JW, Whitley RJ. Clinical practice, Herpes zoster. N Engl J Med 2002;347(5):340-346.
6. Dolin R, Reichman RC, Mazur NIH, et al. Conference Herpes zoster–varicella infection in immunosuppressed patients. Ann intern Med 1978;89(3):375-378.
7. Wall PD. Neuropathic pain and injured nerve central mechanisms. Br Med Bull 1991;47(3):631-643.
8. Huff JC, Drucker JL, Chimmer A, et al. The effect of oral acyclovir on pain resolution in herpes zoster a reanalysis. Med Virol 1993;(Suppl 1):93-96.
9. Esmann V, Gell JP, Kroon S, et al. Prednisolone does not prevent post–herpetic neuralgia. Lancet 1987:2(8551):126-129.
10. Whitley RJ, Weiss H, Gnann JW, et al. Acyclovir with or without prednisone for the treatment of herpes zoster; a randomized, placebo–controlled trial. The national institute of allergy and infectious diseases collaborative antiviral study group. Ann intern Med 1996:125(5):376-383.
11. Van Wijck AJ, Opstelten W, Moons KG, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia, a randomised controlled trial. Lancet 2006:367(9506):219-224.
12. Bowsher D. The effects of pre-emptive treatment of post herpetic neuralgia with amitriptyline a randomized, double–blind placebo-controlled trial. J Pain Symptom Manage 1997:13(6):327-331.
13. Berry JD, Petersen KL. A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. Neurology 2005;65(3):444-447.
14. Wood MJ, Ogan PH, McKendrick MW, et al. Efficacy of oral acyclovir treatment of acute herpes zoster. Am J Med 1988;85(2A):79-83.
15. Gilden DH, Dueland AN, Cohrs R, et al. Preherpetic neuralgia. Neurology 1991;41(8):1215-1218.
16. Watson CPN. Post herpetic neuralgia. Neurol Clin 1998;7:231-248.
17. Watson CPN, Watt VR, Chipman M, et al. The prognosis with postherpetic neuralgia. J Pain 1991;46(2):195-199.
18. Hope- Simpson RE. The nature of herpes zoster a long- term study and a new hypothesis. Proc R Soc Med 1965;58(1):9-20.
19. Burgeon CF, Burgeon JS, Baldridge GD. The natural history of herpes zoster JAMA 1957:164(3):265-269.
20. Brown GR. Herpes zoster correlation of age, sex, distribution, neuralgia and associated disorders. South Med J 1976;69(5):576-578.
21. Wood M. Understanding zoster-associated pain. In: How can the burden of zoster associated pain be reduced. Recommendations from the IHMF workshop Washington DC, Worthing United Kingdom PPS Europe 1993;3-11.
22. Epstein E. Treatment of zoster and post zoster neuralgia by the intralesional injection of triamcinolone: a computer analysis of 199 cases. International Journal of Dermatology 1976;35:762-769.
23. Balfour HH. Varicella zoster virus infectious in immunocompromised hosts: a review of the natural history and management. Am J Med 1988;85(2A):65-73.
24. Bennett GJ. Hypothesis on the pathogenesis of herpes zoster–associated pain. Ann Neurol 1994;35(suppl):S38-41.
25. Devor M. Central changes meditating neuropathic pain. In: Dubner R, Gebbart GF, Bond MR eds. Proceedings of the Vth World congress on pain Amsterdam Elseviere Science 1988;114-128.

26. Morton P, Thompson AN. Oral acyclovir in the treatment of herpes zoster in general practice. N Z Med J 1989;102(863):93-95.
27. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia, a randomized double blind placebo controlled trial. Ann intern Med 1995;123(2):89-96.
28. Beutner KR, Freidmann DJ, Forszpaniak C, et al. Valacyclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Anti Microb Agents Chemother 1995;39(7);1546-1553.
29. Huff JC, Bean B, Balfour HH, et al. Therapy of herpes zoster with oral acyclovir. Am J Med 1988;85(Suppl 2A):84-88.
30. McKendrick MW, McGill JI, White JE, et al. Oral acyclovir in acute herpes zoster. Br Med J 1986;293(6561):1529-1532.
31. Wood MJ, Dworkin RH, Soong SJ, et al. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster a meta-analysis of placebo-controlled trials. Clin infect Dis 1996;22:341-347.
32. Dworkin RH, Perkins FM, Nagasako EM. Prospectus for the prevention of postherpetic neuralgia in herpes zoster patients. Clin J pain 2000;16(suppl2):S90-S100.
33. Neurontin (package insert). New York, Pfizer Inc 2009.
34. Depomed Inc. Depomed announces US food and drug administration approval of Gralise (gabapentin) once daily tablets for treatment of post–herpetic neuralgia. Nasdaq 2011 Available at: http://investor.depomedine. comphonix.zhtml1?c= 9727 6&p=irol–news Article_pf&ID-1521435. Accessed May 4, 2012.
35. Benjamin Beal, Tobias Moeller- Bertram, Jan M Schilling, et al. Gabapentin for once–daily treatment of postherpetic neuralgia: a review. Clinical Interventions in Aging 2012;7:249–255.
36. Bockbrader HN, Wesche D, Miller R, et al. A compression of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin pharmacokinet 2010;49(10):661-669.
37. Drolet M, Brisson M, Schmader K, et al. Predictors of post herpetic neuralgia among patients with herpes zoster: a prospective study. J Pain 2010;11(11):1211-1221.
38. Johnson RW. Zoster–associated pain what is known, who is at risk and how can it be managed? Herpes 2007;14(Suppl 2):30-34.
39. Codere TJ, Katz J, Vaccarino AL, et al. Contribution of central neuro plasticity to pathological pain; review of clinical and experimental evidence. Pain 1993;52(3):258-285.
40. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998:280(12):1837-1842.