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Original Article

Amitriptyline: An effective intervention in Post-herpetic neuralgia prevention? Evidence from a randomized control trial

Muhammad Fahim[1], Hina Khoso[2], Mehtab Alam[3], Jahangir Khan[4], Farah Sagheer[5]

[1] Tehsil Headquarters Hospital TakhtaBhai, Mardan.
[2] Dermatology Department, Shaheed Mohtarma Benazir Bhutto Medical University/ Chandka Medical Collage, Larkana.
[3] Department of Neurology, Medical Teaching Institute/ Lady Reading Hospital Peshawar.
[4] Department of Dermatology, AL ADAN Hospital, Kuwait.
[5] Deputy CEO, Post Graduate Medical Institute, Peshawar.

Abstract

Background Postherpetic neuralgia (PHN) is a chronic painful condition of neuronal origin lasting more than 3 months in the previously involved dermatome by herpes zoster. PHN remains the most common and debilitating complication of herpes zoster affecting the quality of life of such patients. A variety of symptoms have been reported including pain, allodynia, hyperalgesia, paresthesia, and dysesthesia, in the absence of active herpes lesions. Although there are several therapeutic options for PHN, there is little information available regarding its prevention. This study aimed to fill this research gap and explore the role of amitriptyline in preventing PHN.

Objective To evaluate the efficacy of Amitriptyline in the prevention of Post Herpetic Neuralgia (PHN).

Methods A total of 120 herpes zoster patients, presenting within 3 days were selected. Patients were split into two groups. Group A received 25 mg amitriptyline along with famciclovir, while group B used only oral famciclovir. Both groups were given other analgesics like Gabapentin, topical analgesics, and NSAIDs on a need basis. Patients were evaluated at monthly intervals and the final pain scores were calculated after 3 months.

Results At the baseline, patients in the significant pain category were comparable in both groups. After 3 months the number of such patients in Group B was higher. Similarly, there was clear disparity between the two groups regarding the number of patients achieving good/ excellent pain reduction (p valve<0.05).

Conclusion This study showed that oral Amitriptyline started concomitantly with antivirals significantly reduced the incidence of post-herpetic neuralgia.

Key words
Amitriptyline, Herpes zoster, Post Herpetic Neuralgia.

Introduction

Herpes zoster (HZ), often known as shingles, is a frequent condition characterized by a painful, unilateral vesicular eruption that is brought on by the reactivation of a latent varicella zoster virus in the dorsal root or cranial nerve ganglia.[1] It usually affects elderly patients, mostly those having comorbidities like diabetes, etc. The

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Address for correspondence
Dr. Mehtab Alam, MBBS, FCPS (Neurology), Assistant professor, Department of Neurology, Medical Teaching Institute/ Lady Reading Hospital, Peshawar.
Ph: +923450595660; Email: mehtab39@gmail.com

average age of onset is 50-60 years and the lifetime risk is 30%.[2] Herpetiform vesicles suddenly appear on the skin, affecting the unilateral dermatomes. Rarely, it can involve multiple dermatomes and can be generalized, especially in immunocompromised patients.[3] The Dermatomal involved in the order of frequency are thoracic 53%, cervical 20%, trigeminal including ophthalmic 15%, and lumbosacral 11%.[4] The eruption is commonly preceded by prodromal symptoms like numbness, paresthesia, etc.

In acute stages the herpes associated pain can be throbbing, stabbing, or aching. The skin lesions resolve in a couple of days and are associated with the reduction/ resolution of pain in many patients.[5] Even after the lesions have healed, some individuals still complain of pain. The most frequent herpes zoster consequence, post herpetic neuralgia (PHN), is the name given to this pain and discomfort. There are many definitions for post herpetic neuralgia but the widely accepted is as pain persisting for longer than 120 days/ 3 months in the previously involved dermatomes after the healing of skin lesions.[6] Other consequences of herpes zoster include dissemination, secondary bacterial infection, scarring/ disfigurement, nerve palsies, encephalitis, meningitis, hepatitis, etc.[7]

Post herpetic neuralgia is a debilitating condition leading to physical, economic, and psychosocial distress. It may take several forms, including allodynia (nonpainful stimulus perceived as painful), hyperpathia (slightly painful stimulus perceived as very painful), and dysesthesia (abnormal sensation with no stimuli).[8] Elderly patients especially those above 70 years are commonly affected, mostly women. Other risk factors include severe signs and symptoms at shingles onset, immunosuppression, diabetes mellitus, autoimmune diseases, and personality disorders.[9] It may take several months and years to resolve and many people continue to be refractory to the existing therapies despite numerous advancements in treatment.

According to evidence with currently available treatments, pain management in PHN is often difficult and necessitates a multidisciplinary approach.[10] Most patients need a combination of therapies and these are tailored according to each patient's requirements, comorbidities, and tolerability. Commonly used drugs are gabapentin, amitriptyline, valproic acid, carbamazepine, topical lidocaine, topical capsaicin, NSAIDs, and opioids.[11]

Very little data about the preventive measure is available for PHN. First of all, a live attenuated varicella zoster vaccine (VZV) is administered during the childhood period to reduce the occurrence of chickenpox, resulting in a lower occurrence of HZ reactivation and subsequent PHN.[12]

Secondly, to decrease the risk of PHN, another dose of VZV is given to patients above 60 years of age. As PHN commonly involves elderly patients, this can lessen the total burden of herpes zoster and subsequent PHN.[13] Unfortunately, this approach has not been executed on a large-scale basis in third world countries and Pakistan due to various reasons like financial problems and lack of awareness.

Timely use of antivirals especially within 72 hours can lower the likelihood of PHN. Studies suggest that antiviral medications can reduce the viral load in the dorsal root ganglia and limit the virus' production. These agents shorten the duration of viral shedding, speed up rash healing, lessen the severity and duration of acute discomfort, and lower the possibility of developing PHN. Compared to Acyclovir, Famciclovir and Valacyclovir showed better results.[14]

Finally, there is some evidence that amitriptyline helps in the prevention of PHN. Amitriptyline is a tricyclic (TCA) antidepressant. It works mainly by preventing the reuptake of serotonin and norepinephrine neurotransmitters.[15] The other mechanisms of action of amitriptyline include monoamine reuptake inhibition, receptors and voltage-gated sodium/ calcium channel modulation, and gene transcription.[16] There is a possibility that several of amitriptyline's effects on various nociceptive and sensory processes at central and peripheral regions may work together to reduce the distinctive symptoms of neuropathic pain.

Neuropathic pain has got many pathogenetic mechanisms. For instance, when inflammatory signaling molecules cause the phosphorylation of tetrodotoxin-resistant sensory neuron-specific (SNS) sodium ion channels, peripheral nociceptors may become sensitized.[17] When these sensitized nerves are stimulated, they generate a significant evoked potential and transmit that signal to the central nervous system. As a result of this, these nociceptors activate more easily for transduction. Additionally, the expression of receptors and neurotransmitters may change as a result of inflammation or peripheral axon injury. The clinical responsiveness to pain may also be influenced by these possibly long-lasting changes. The dorsal horn neurons and dorsal root ganglia may both exhibit altered gene transcription.[18]

Looking at all of these contributing mechanisms in neuropathic pain, the use of amitriptyline seems logical for the treatment and prevention of PHN. Many studies have shown its efficacy in PHN treatment but very sparse data is available on its preventive role. This study aimed to fill this research gap.

Materials and Methods

Diagnosis of herpes zoster was confirmed on the basis of history and examination. All patients presenting to skin OPD with herpes zoster were considered for enrolment in this study (after approval: number 23/THQ, dated 16.08.2022). Following the application of the inclusion and exclusion criteria, 120 patients in total were chosen and split into two groups; each consisting of 60 patients. Group A received 25mg of amitriptyline once daily at night along with standard doses of famciclovir, while Group B received famciclovir only. Amitriptyline was continued for 3 months while famciclovir was given for only 7 days. All patients in both groups also used supplementary analgesics on a need basis like NSAIDS, topical analgesics/ polyfax plus skin ointment, and gabapentin. Subjective assessment of pain severity was carried out at baseline, monthly, and finally after 3 months using, a descriptive pain scale, visual analog pain scale. For the determination of efficacy using the visual analogue scale, only moderate, severe, very severe, and worst possible pain was considered as significant at the start and end of the study.

Inclusion criteria All patients between the ages of 20 and 80 who consented to participating in the trial and who presented within 72 hours of the onset of shingles.

Exclusion criteria Patients experiencing complications associated with herpes zoster (ocular involvement, extensive disseminated infection, motor neuropathies, involvement of more than two contagious dermatomes, and other complications like encephalitis and cerebrovascular sign and symptoms), HIV-positive individuals, pregnant women, nursing mothers, patients taking concurrent immunosuppressive medication, patients with abnormal renal function tests, diabetes, or any other co-morbidity were all excluded. Similarly, patients with specific contraindications to amitriptyline like symptoms of prostatism, constipation, blurred visions, and a history of

allergic reactions were not enrolled in this study.

Data analysis Statistical software for social science (SPSS Version 24) was used to enter and analyze the data. The mean & SD were calculated for age and duration of disease at baseline and 6 months of treatment. Both groups were compared by age, gender, Visual analogue, and pain reduction scores. Chi-square analysis was used to compare the efficacy in both groups, using a two-sided P <0.05 as significant.

Results

Overall female patients were more in number. The basic clinical and demographic data is shown in **Table 1**. The mean age and duration of disease were 50.23±11.8 years and 2.466± 0.724 days in Group A and 46.84±10.3 years and 2.58±0.64 days in Group B respectively. Pain severity was assessed based on descriptive, visual analogue, and pain reduction scores (**Table 2A-2C**).

The number of patients in the significant pain category (moderate, severe, very severe, and worst possible pain) was comparable in both groups. After 3 months based on the visual analogue score, 46 patients in Group A and 27 patients in Group B reverted to the No pain/ Mild pain category (p-value=0.0126, **Figure 1**).

Similarly using pain reduction score, greater percentage of patients in Group A achieved good and excellent pain reduction p-value=.00008 (**Figure 2A&2B)**.

Discussion

Herpes zoster is an acute onset vesicular eruption, with life time risk of 10-30%, involving mostly the elderly population.[19] It has got multiple complications but PHN is the most important and

Table 1 Clinical and demographics data.

Parameter	*Amitriptyline +Famciclovir (Group)*	*Famciclovir without Amitriptyline (Group)*	*P-value*
No. of patients	60	60	
Gender			
Male	30	27	0.5834
Female	30	33	
Age (in years)	50.23±11.8	46.84±10.3	0.0963
Duration of disease (Onset of rash) in days	2.466 ±0.724	2.58± 0.64	0.3627
Dermatomes involved			
Thoracic	27	24	
Lumber	12	15	
Cervical	7	4	
Cranial Nerves	14	17	
Severity of pain	Baseline		
No pain	0	1	
Mild pain	4	7	
Moderate pain	13	16	
Severe pain	19	14	
Very severe pain	15	17	
Worst possible pain	9	5	

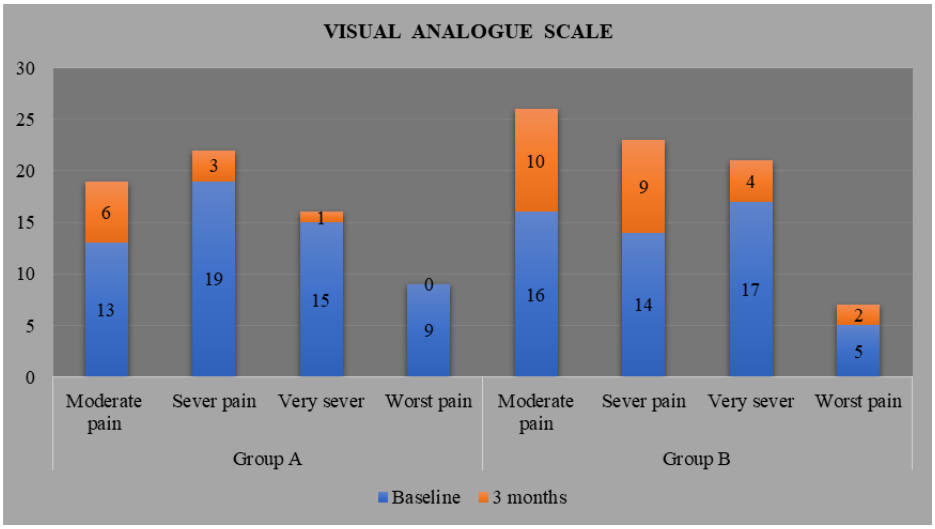

Figure 1 Number of patients in significant pain category at baseline and after 3 months.

Table 2

A. Descriptive pain Score	B. Pain reduction score
0=No pain	0=No change
1=Mild pain	1=Slight pain reduction
2=Distressing pain	2=Moderate pain reduction
3=Sever pain	3=Good pain reduction
4=Horrible pain	4=Excellent pain reduction
5=Excruciating pain	

C. Visual analogue scale

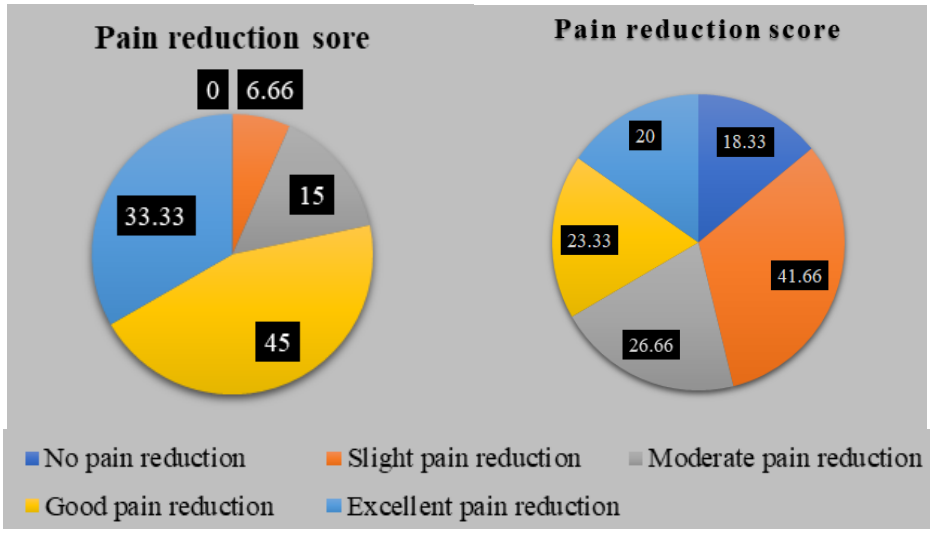

Figure 2 A&B showing Percentage of patients achieving variable pain reduction in both groups.

significantly affects the quality of life. PHN is a potentially crippling and frequently untreated kind of neuropathic pain that disproportionately affects vulnerable populations, such as the elderly and the immunocompromised. It is defined as persistent pain in as specific dermatomes lasting more than 3 months after the onset of shingles. Normally PHN pain is unilateral, localized, and chronic, although it can also be persistent, intermittent, spontaneous, or triggered.[20] Sleep and daily activities are likely to be disrupted by PHN. Many options are available for PHN neuralgia treatment including tricyclic antidepressants, anticonvulsants (gabapentin and pregabalin), topical lidocaine (5% patch), various formulations of opioids, and topical capsaicin (cream or 8% patch) and NSAIDS but limited data exists regarding PHN prevention.[21] This study aimed to fill this research gap.

A total of 120 participants were enrolled in this study. The basic clinical and demographic data are shown in **Table 1**. The mean duration of disease and dermatomal involvement was comparable in both groups. The intensity of pain was evaluated using various questionnaires like Descriptive Pain score, visual analog score, and pain reduction score. After 3 months, Group A achieved better pain control in terms of visual analogue score and pain reduction score with p-value of <0.05.

As PHN is preceded by herpes zoster, theoretically, prophylaxis of chickenpox and herpes zoster can prevent PHN. A live attenuated Varicella Zoster vaccine's effectiveness has been assessed by studies when given to children and adolescents with 2 doses confirming more than 95% immunity. Similarly, post-exposure prophylaxis with vaccination, IV immunoglobulin, and antivirals can prevent and modify the courses of disease and subsequent complications.[22-24]

As the incidence of PHN is higher in elderly and immunocompromised patients, a live attenuated vaccine recommended by CDC is administrated to patients above 60 years of age regardless of previous history of shingles. A systematic review by Anna M Z Gagliard *et al.* envaulted the efficacy of the zoster vaccine in the elderly. Based on data from one large trial with 38,546 individuals aged 60 or over, it appeared that participants who received the vaccine experienced a reduced incidence of herpes zoster than those who received a placebo at up to three years of follow-up with risk ratio (RR) of 0.49 and 95% confidence interval (CI).[25]

A Cochrane review by Daniel S *et al.* included six randomized control trials and 1211 patients. Most of the patients received oral acyclovir and few were given famciclovir within 72 hours of shingles onset. The positive outcome in very few studies may be due to different definitions for PHN, not considering the quality of pain in addition to pain reduction in the outcome.[26]

In a randomized control trial by K R Beutner *et al;* patients were split into 2 groups. One group revived oral acyclovir 800mg 5 times a day while the other group received valacyclovir at a dosage of 1,000 mg 3 times daily. All patients continued the antivirals for at least 7 days. In comparison to acyclovir, the intent-to-treat analysis revealed that using valaciclovir for 7 or 14 days significantly sped up the resolution of herpes zoster-related discomfort (P=0.001 and P=0.03 respectively). The median pain duration was lesser in vacyclovir treated group. Additionally, treatment with valaciclovir also significantly lowered the proportion of patients with pain persisting for 6 months or more.[27]

Different doses of famciclovir were assessed in a randomized, double-blind, placebo-controlled, multicenter trial. Three groups of patients were given 500mg, 750mg of famciclovir, and a placebo respectively. Therapy was continued for 7 days. Famciclovir had a safety profile that was comparable to a placebo and was well tolerated. Famciclovir sped up lesion healing and shortened the duration of viral shedding. At the end of 5 months, Patients on famciclovir experienced postherpetic neuralgia resolution that was roughly two times faster than placebo. The results were statistically significant (P=0.02 and 0.01, respectively). The median postherpetic neuralgia duration was cut by about 2 months.[28]

In another randomized control trial conducted in Lahore, 2 different doses of famciclovir were used to see the impact on PHN. 250mg and 500mg of famciclovir were received by patients in 2 groups (15 patients in each group) 3 times a day for 7 days. At the 2, 4, and 12-week follow-ups, the statistical effectiveness of both dosage groups in lowering pain was comparable. The difference between pain score and skin lesions at baseline and after 3 months was statistically significant in both groups (p=<0.05).[29]

D Bowsher *et al.* evaluated the efficacy of amitriptyline for the prevention of PHN. 38 patients were given amitriptyline 25mg once a day at night for 3 months consecutively, while 34 patients received a placebo only. A total of 26 patients in both groups received oral acyclovir, depending on presentation within 48 hours of shingles onset and the treating physician's priorities. After 6 months, 82.2% of patients in the amitriptyline group and 64.7% of patients in the placebo group were pain free regardless of the use of acyclovir (P value;0.005).[30]

Conclusion

This study concluded that amitriptyline in combination with antivirals significantly reduces the incidence of PHN compared to antivirals alone.

Limitations of the study This study was limited by the small sample size, so generalizability of results may not be possible on a larger population. Secondly, long term follow up was not carried out to see the impact on disease remission and relapse.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

MF, HK: Conceptualization, data collection, final approval of the version to be published.

MA: Critical review, final approval of the version to be published.

JK, FS: Critical review, data analysis, final approval of the version to be published.

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