Prednisolone can Prevent Post-Herpetic Neuralgia in Post-Kidney Transplant Recipient

Mohammad Ahmed Saraya[1], Mariam Abdulrhman Al-Fadhli[2] and Jafar Abdulrida Qasem[3]

[1]*Department of Tropical Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt.*
[2]*Department of Medicine, Infectious Disease Hospital, Ministry of Health, Kuwait.*
[3]*Department of Applied Medical Sciences, College of Health Sciences, Public Authority for Applied Education and Training, (PAAET).*

Corresponding Author
Mariam Al-Fadhli

Mobile:
+965 99660936

E mail:
medicine209@gmail.com

Key words:
Kuwait, Prednisolone, herpes zoster, post herpetic neuralgia

Background and study aim: Post-herpetic neuralgia (PHN) is a neuropathic painful condition that is one of the most frequent complications of an acute herpes zoster infection. Till now, there is no general agreement on the definition of PHN. Some studies described a wide range of definitions, including any pain that comes after disappearing of the herpes zoster rash, whereas other studies applied the definition of pain that persist for more than one or two months after the onset of rash. The aim of this study was to assess the effect of oral prednisolone with antiviral therapy on prevention of post-herpetic neuralgia in post-kidney transplant recipient.

Patients and methods: 40 patients were divided into two groups, the first one (group A) involved 20 patients who had renal transplant within the past five years and have received oral prednisolone (10 mg/day) and the second one (group B) involved also 20 patients but they are immune-competent without co-morbidity. Follow up was done at one, three and six months to assess the pain.

Results: At time of admission and discharge, there was significant difference between group A and group B as regard zoster pain. The same significance was observed between two groups during follow up after one and three months and not observed after six months.

Conclusion: Oral corticosteroid can promote modest benefits in decreasing the pain of herpes zoster and the incidence of PHN in post-kidney transplant recipient.

INTRODUCTION

Shingles, or herpes zoster, may occur at any stage in a person's life. Herpes zoster is the clinical manifestation of the reactivation of varicella zoster virus (VZV) which has remained latent within dorsal root ganglia, usually contracted after getting of chickenpox in early life. VZV can be reactivated only once in a lifetime, with the incidence of second attacks being <5% [1]. Herpes zoster (HZ) usually occurs in later life (as T cell immunity to the virus wanes) and in patients who have immune-suppression of T cell. The aims of treating shingles or HZ are to accelerate rash healing, control acute pain, decrease the risk of post-herpetic neuralgia (PHN), and minimize complications. An additional objective is to reduce the risk of visceral and cutaneous dissemination of the VZV, especially for immune-suppressed patients **[2]**.

PHN is a neuropathic painful condition which is the most frequent complications of an acute herpes zoster infection. Three patterns of pain are described as follows. First one, pain at presentation is acute pain and can be resolved over the first 30 days. Second one, and the most debilitating form of pain, is post-herpetic neuralgia. Many definitions of PHN have been applied over the past 30 years and up to date, there is no general agreement on the definition of PHN. The US Food and Drug Administration (FDA) defined PHN as pain which has not resolute 30 days after disease onset. An alternative definition, including any pain which follows disappearance of the herpes zoster rash [3]. The third pattern of pain is that

of zoster-associated pain, whereby pain is viewed as a continuous from the time of acute zoster until its complete resolution, if it occurs. However, recent models of pain resolution and statistical analysis suggest that the most suitable definition of PHN is pain that remains 90 days or more after the onset of HZ rash **[4]**.

Corticosteroids might minimize nerve damage because they have a potent anti-inflammatory action and thereby relieve or prevent the pain of people suffering from this condition. It is theorized that treatment with steroids before the PHN develops may reduce the risk of PHN developing **[5]**.

We aimed in this study to assess the effect of oral prednisolone with antiviral therapy on prevention of post-herpetic neuralgia in post-kidney transplant recipient.

PATIENTS AND METHODS

We undertook 40 patients were diagnosed as herpes zoster at Infectious Disease Hospital (IDH) which is the only tertiary infectious hospital in Kuwait. Diagnosis of herpes zoster was based on the presence of the characteristic skin lesions that begin as a maculopapular rash that follows a dermatomal distribution, commonly referred to as a "belt-like pattern". The maculopapular rash develops into vesicles with an erythematous base.

Patients were excluded if they had a known acquired or congenital immunodeficiency, liver cell failure, kidney failure, peptic ulcer, or skin infections.

The patients were classified into two groups, the first one (group A) involved 20 patients who had renal transplant within the past five years and have received oral prednisolone (10mg/day) and the second one (group B) involved also 20 patients but they are immune-competent without co-morbidity. All patients were subjected to history taking and thorough clinical examination. We measured complete blood count (CBC), kidney profile (KP), liver function test (LFT), blood glucose, C-reactive protein (CRP) and levels of the pro-inflammatory cytokine interleukin-6 (IL-6) (Biomedix medical group, Synlab, German) on the day of presentation and on the day of discharge from the hospital. Follow up was done at one, three and six months to assess the pain.

All patients in both groups received acyclovir intravenously in proper dose according to body weight for 7 to 10 day **[6]**.

Statistical analysis :

The statistical package for social sciences (SPSS) version 8.0 software was used for analysis the data. The t-test was used to evaluate the significance of differences between mean values of the study variables. The significance of differences between proportions was performed using the Chi-square test. Significant differences were expressed at $P<0.05$.

RESULTS

From September, 2013, to November 2014, we enrolled 40 patients in this study and were classified into two groups, group A (post renal transplant patients) and group B (patients without co-morbidity); each of them involved 20 patients. 26 (65%) of 40 patients in both groups A and B are males and 14 (35%) are females.

The mean length of patient stay in the hospital in group A was 9.5 days (±0.76) compared with 7.15 days (±0.98) in group B. Length of hospital stay differed significantly between two groups (p-value = 0.02). There was significant increase in the duration of rash in group A as compared with group B (Table 2).

At time of admission, significant differences were observed between group A and group B as regard C-reactive protein, interleukin-6 concentrations and zoster pain (Table 1). At time of discharge, the same significant in C-reactive protein, interleukin-6 concentrations and zoster pain were observed between two groups (Table 2).

Follow up after one month, there were two patients had PHN in group A and nine patients in group B and there were significant difference between both groups (Table 3). Follow up after three months, there were no patients had PHN in group A and there were six patients had PHN in group B and there were significant difference between both groups (Table 3). Follow up after six months, no significant difference regarding PHN were observed between groups.

Table (1) : Comparison between studied groups at time of admission

	On admission		
	Group A N (20 patients)	**Group B N (20 patients)**	**P-value**
Age	49.51±6.7	50.40±7.1	0.51
Sex			
Male n (%)	13 (65%)	13 (65%)	1.0
Female n (%)	7 (35%)	7 (35%)	1.0
ALT	41.5±48.3	39.2±47.3	0.71
AST	51.0±36.8	48.1±31.7	0.65
CRP	22.05±5.04	45.05±5.05	0.000
IL6	8.57±4.09	19.79±3.07	0.000
Plt	162.95±31.31	163.45±33.16	0.94
WBCs	5.9±1.15	6.23±1.25	0.24
S. creatinine	117.5±14.12	101.5±13.23	0.21
Herpes Zoster site:			
Thoracic	13 (65%)	10 (50%)	0.12
Lumber	6 (30%)	7 (35%)	0.73
Sacral	1 (5%)	3 (15%)	0.32
Pain at presentation:			
No pain	10 (50%)	0 (0%)	0.000
Mild	7 (35%)	4 (20%)	0.01
Moderate	3 (15%)	11 (55%)	0.001
Severe	0 (0%)	5 (25%)	0.001

Table (2) : Comparison between studied groups at time of discharge

	On discharge		
	Group A N (20 patients)	**Group B N (20 patients)**	**P-value**
ALT	36.2±46.2	34.5±45.3	0.74
AST	49.0±34.6	45.1±36.4	0.71
CRP	12.06±3.3	18.04±3.1	0.001
IL6	6.31±2.02	11.29±2.07	0.01
Plt	180.73±22.4	172.75±25.6	0.61
WBCs	6.3±1.2	6.9±1.3	0.89
S. creatinine	119.4±12.1	101.5±14.3	0.05
Duration of rash	13.6±0.42	8.5±0.54	0.01
Length of hospital stay	9.5±0.76	7.15±0.98	0.02
Pain at discharge:			
No pain	13 (65%)	6 (30%)	0.001
Mild	6 (30%)	3 (15%)	0.001
Moderate	1 (5%)	8 (40%)	0.000
Severe	0 (0%)	3 (15%)	0.001

Table (3) : Comparison between studied groups at 1, 3, 6 months regarding the pain

	Follow up		
	Group A N (20 patients)	**Group B N (20 patients)**	**P-value**
Pain at one month:			
No pain	18 (90%)	11 (55%)	0.001
Mild	2 (10%)	6 (30%)	0.01
Moderate	0 (0%)	3 (15%)	0.01
Severe	0 (0%)	0 (0%)	1.0
Pain at three months:			
No pain	20 (100%)	14 (70%)	0.001
Mild	0 (0%)	5 (25%)	0.001
Moderate	0 (0%)	1 (5%)	0.97
Severe	0 (0%)	0 (0%)	1.0
Pain at six months:			
No pain	20 (100%)	19 (95%)	0.96
Mild	0 (0%)	1 (5%)	0.97
Moderate	0 (0%)	0 (0%)	1.0
Severe	0 (0%)	0 (0%)	1.0

DISCUSSION

Post-Herpetic Neuralgia (PHN) is noted in 9–45% of all cases of herpes zoster (HZ) and the incidence has been increased to 50–60% among elderly or immune-suppressed patients **[7]**. PHN is simply defined as a form of nerve pain (neuritis, neuropathy) that persists in the area of the rash once the HZ lesions have healed **[3].**

There is consensus for the need of early therapy that prevents virus multiplication thereby decreasing damage to the dorsal horn, dorsal root ganglion, and peripheral sensory receptors in the skin. The early treatment of herpes zoster can not only treat the acute infection but can also prevent the onset of PHN by limiting viral induced nerve damage **[7].**

The difficulties in verifying the validity of the use of acyclovir and steroids in treatment of HZ are due to lack of standardization of concepts. So, we chosen group A to be the patient group because they have already given corticosteroid. The likelihood of patients suffering from HZ after renal transplant (RTX) to develop PHN or a disseminated VZV disease is up to nine times increased compared with the general population **[8]**. Considering that the patients with end-stage renal disease (ESRD) and on dialysis have impaired cellular immunity **[9]** and that cellular immunity will be massively suppressed in these patients at the time of transplantation by current induction therapies **[10]**.

The results of this study demonstrate that the administration of intravenous acyclovir and low dose of corticosteroid in group A can prevent the development of post-herpetic neuralgia (PHN) to a significant greater extent than intravenous acyclovir only in group B at time of discharge, after one month and after three month and this difference is not observed after six months (Table 2 & 3). As regard of acute zoster pain, the difference between the studied groups was observed as early as at time of presentation.

Many authors agree that the use of steroid is effective for both the acute phase pain of herpes zoster and for the prevention of PHN, and they attribute its efficacy to the potent anti-inflammatory effects and to lysosomal protection which could decrease neuronal damage **[7].** Some authors, however, doubt the efficacy of steroid and propose that steroids promote the risk of herpes dissemination **[5]**. In this study, the dermatomal distributions in patients of group A who are immune-compromised and with low dose of corticosteroid do not support this later viewpoint that the use of steroid is ineffective and contribute to systemic dissemination.

Despite, we compare between immune-compromised patients in group A and immune-competent patient in group B, the risk of

development of PHN in group B is significantly higher than in group A.

The oral administered of corticosteroids with acyclovir has been shown to decrease the pain of herpes zoster. The likely pathogenesis includes reducing the degree of neuritis caused by active infection and, possibly, reducing residual damage to affected nerves **[11]**.

Some studies were designed to assess the effectiveness of prednisolone therapy in preventing PHN and have demonstrated that the pain decreased at three and 12 months **[5]** .While other studies have shown no benefit **[11]**.

In summary, this study demonstrated that the patients in group A, who treated with acyclovir and low dose of corticosteroid, are not at higher risk for developing PHN than the immune-competent patients in group B, who treated only with acyclovir.

CONCLUSION

An orally administered low dose of corticosteroid can promote modest benefits in reducing the pain of herpes zoster and the incidence of post-herpetic neuralgia in post-kidney transplant recipient.

Funding: None.
Conflicts of interest: None.
Ethical approval: Approved.

REFERENCES

1. Cunningham AL,Dworkin RH. The management of post-herpetic neuralgia. *BMJ;* 2000, 321(7264): 778–779.
2. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med;* 2002, 347: 340–6.
3. Whitleya RJ, Volpib A, McKendrickc M, van Wijckd A, Oaklandere AL. Management of herpes zoster and post-herpetic neuralgia now and in the future. *Journal of Clinical Virology;* 2010, (48) S1, S20–S28.
4. Arani RB, Soong S-J, Weiss HL, Wood MJ, Fiddian PA, Gnann JW, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. *Stat Med*; 2001, 20: 2429–39.
5. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing post-herpetic neuralgia. *Cochrane Neuromuscular Disease Group;* 2013, Published Online: 28 MAR; CD005582.
6. dos Santos MC ,Alecrim.MGC. Varicella Pneumonia in an Adult. *N Engl J Med;* 2010, 362:1227.
7. Pasqualucci A, Pasqualucci V, Galla F, De Angelis V, Marzocchi V, Colussi R, et al . Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. *Acta Anaesthesiol Scand*; 2000, 44: 910–918.
8. Arness T, Pedersen R, Dierkhising R, Kremers W, Patel R . Varicella zoster virus-associated disease in adult kidney transplant recipients. Incidence and risk-factor analysis. *Transpl Infect Dis* 2008, 10: 260-268.
9. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008, 3:1526-1533.
10. Litjens NH, Huisman M, van den DM, Betjes MG.Impaired immune responses and antigen-specific memory CD4 + T cells in hemodialysis patients. *J Am Soc Nephrol*; 2008, 19:1483-1490.
11. Stankus SJ, Dlugopolski M,Packer D. Management of Herpes Zoster (Shingles) and Postherpetic Neuralgia. *Am Fam Physician*. 2000 Apr 15, 61(8):2437-2444.

Peer reviewer:Nahla Elgammal, Professor of Tropical Medicine, Faculty of Medicine, Zagazig University, Egypt.

Editor: Tarik Zaher, Professor of Tropical Medicine, Faculty of Medicine, Zagazig University, Egypt