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Amitriptyline Versus Pregabalin in Post Herpetic Neuralgia: A Randomized Clinical Trial

Postherpetik Nevraljide Amitriptilin ile Pregabalinin Karşılaştırılması: Bir Randomize Klinik Çalışma

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Abstract

Objective: Post herpetic neuralgia is a most common complication of herpes zoster which is difficult to treat. Significant beneficial effects found when treated with antiviral, tricyclic antidepressant, anticonvulsive like gabapentine and pregabalin, opioid and non opioid analgesic etc. Primary prevention can also be done with vaccine. The aim of this randomized comparative study was to establish clinical efficacy with amitriptyline and pregabalin.

Methods: An open ended randomized clinical trial was conducted to compared clinical efficacy of amitriptyline (n=25) and pregabalin (n=25). Amitriptyline was given 25 mg once daily and pregabalin 75 mg twice daily. Total period of treatment were 6 month and patients were reviewed at the end of 2 months, 4 months and 6 months to evaluate the degree of improvement in pain perception and any adverse reaction.

Results: Four types of patients were included in this study and among them thoracic type was the commonest (54%). It was followed by cervical (24%), trigeminal (16%) and lumbosacral types (6%). According to VAS score, satisfactory significant improvements in pain perception was observed at the end of 2 months (36%vs 8%, $p<0.05$) and 4 months (61.9%vs 27.8%, $p<0.05$) in pregabalin group than amitriptyline group. The chances of improvement more than 6 times and 4 times higher in patients with pregabalin group than those in amitriptyline group. There is no significant improvement difference was noticed at the end of 6months between groups. However, improvement was 89%(OR=1.89, 95% CI: 0.53-6.68) higher in pregabalin group than amitriptyline group. More importantly dizziness was the commonest side effect in pregabalin group while dryness of mouth was the commonest side affect in amitriptyline group.

Conclusion: In conclusion, therapy with pregabalin is better compare to amitriptyline in post herpetic neuralgia. However a similar study with larger augmentation is required to establish the findings.

Key words: Amitriptyline, clinical trial, Herpes zoster, pregabalin, post-herpetic neuralgia

Özet

Amaç: Postherpetik nevralji herpes zosterin tedavi edilmesi güç ve en yaygın komplikasyonudur. Antiviral, trisiklik antidepresan, gabapentin ve pregabalin gibi antikonvülzanlar ve opioid olmayan analjezikler gibi ilaçlarla tedavinin kayda değer yararlı etkileri görülmektedir. Primer koruma aşı ile de sağlanabilir. Bu randomize karşılaştırmalı çalışmada amitriptilin ve pregabalinin klinik etkinliğinin ortaya konması amaçlandı.

Yöntemler: Amitriptilin (n=25) ve pregabalinin (n=25) klinik etkinliğini karşılaştırmak amacıyla açık uçlu randomize klinik bir çalışma yürütüldü. Amitriptilin günde tek doz 25 mg, pregabalin günde iki kez 75 mg olarak verildi. Toplam tedavi süresi 6 ay idi ve ağrı algılanmasındaki düzelmenin derecesini ve herhangi advers bir reaksiyonu değerlendirmek üzere hastalar 2, 4 ve 6. ayın sonunda denetlendi.

Özet

Bulgular: Çalışmaya dört tip hasta dahil edildi ve bunların arasında en sık olan torasik tipti (%54). Bunu sırasıyla servikal (%24), trigeminal (%16) ve lumbosakral (%6) tipler takip ediyordu. VAS skoruna göre, ağrı algılamasında 2. ayın sonunda pregabalin grubunda amitriptilin grubuna kıyasla tatmin edici bir düzelme gözlendi (%36'ya karşın %8, p<0.05). Düzelmedeki değişiklikler pregabalin grubunda amitriptilin grubuna göre 6 kat daha fazlaydı. Gruplar arasında 4 ve 6. ayın sonunda anlamlı bir düzelme farkı gözlenmedi. Bununla birlikte, pregabalin grubunda düzelme %89 (OR=1.89, %95 GA: 0.53-6.68) idi ve amitriptilin gruba göre daha yüksekti. Önemli olarak, pregabalin grubundaki en yaygın yan etki baş dönmesi iken, amitriptilin grubundaki en yaygın yan etki ağız kuruluğu idi.

Sonuç: Sonuç olarak, postherpetik nevraljide pregabalin ile tedavi amitriptiline göre daha üstün bulundu. Bununla birlikte, bunu pekiştirmek için daha büyük ölçekli benzer çalışmalara gereksinim vardır.

Anahtar kelimeler: Amitriptilin, klinik çalışma, Herpes zoster, pregabalin, postherpetik nevralji

Introduction

Post herpetic neuralgia is a complication of shingles (herpes zoster) which is caused by varicella zoster virus. It is results from a combination of inflammatory and viral damage of primary afferent sensory nerve fibre. Most case of shingles clears up, within a few weeks. But if the pain persists long after the rash and blister disappeared, it's called post herpetic neuralgia (PHN). But sometimes PHN can begin in the absence of herpes zoster (HZ), in which case zoster sine herpetic is presumed.

Three phases of pain present in PHN: acute pain (within first 30 days), sub acute pain (between 30 to 120 days) and chronic pain (lasting >120 days) (1). About one million of cases of HZ occur in the USA per year and the incidence usually increases with the population ages (2). Amongst these patients PHN may develop 9-34% (3). Increased age, increased severities of acute pain, greater extend of rash, and the presence of prodromal symptoms will increase PHN development and severity (4).

PHN is thought to be nerve damage caused by varicella zoster virus. The damage causes nerves in the affected dermatomic area of the skin to send demormal signals to the brain. These signals may convey different types of pain. There are three basic types of pain has been described as (a) constant, monotonous, usually burning or deep aching pain: (a) shooting or lancinating (neuritic pain) (c) triggered pain.

No laboratory work is usually necessary to confirm the diagnosis of the patient. Cerebrospinal fluid study viral culture, antibody titre of herpes zoster and MRI study sometime needed for better evaluation of patient.

Treatment of post herpetic neuralgia depends in the type and characteristic of the pain experienced by the patient. Pain control is essential for management of patient care. There is no single treatment that relieves all patients. In many cases, it may take a combination of treatment to reduce the pain.

Possible Option of Medicines:

Antiviral Agents: acyclovir, valacyclovir and famcyclovir are highly selective for thymidine kinase, enzyme encoded by herpes zoster virus and ultimately viral replication. By inhibiting viral replication, the duration of viral shedding and time to rash healing, severity and duration of the acute pain and risk of progressing of PHN are reduced (5).

Anticonvulsant: These agents are used to manage severe muscle spasms and sedation in neuralgia. They have central effect on pain modulation. Amongst the different anticonvulsants, phenytoin, carbamazepine, gabapentin, pregabalin etc. are used to manage PHN. Gabapentin and pregabalin binds to the α-2δ subunit of voltage gated calcium channels decreasing calcium influx and inhibited the release of excitation neurotransmitter. Both of these drugs reduce the pain significantly. Pregabalin was approved by FDA and given with the dose of 150-600 mg per day with divided doses (6). Common adverse effect includes dizziness, somnolence, blurred vision, weight gain and peripheral edema.

Antidepressants: Tricyclic antidepressants were the first agent to demonstrate clinical efficacy and was considered the first line therapy for many years (7). They have a complex group of drugs that have central and peripheral anti cholinergic effects as well as sedation. They have central effect on pain transmission and block active re-uptake of nor epinephrine and serotonin. Amongst the tricyclic antidepressant, amitriptyline and nortriptyline are commonly used. Side effects include dry mouth, sweating, dizziness, orthostalic hypotension, fatigue, constipation, problem with micturation and cardiac disturbances.

Analgesic: Locally applied topical agents – aspirin (8), gallium maltolate (9), lidocaine skin patch (10). Systematically delivered medicines are non-opioid and opioids or combinations of both. Although corticosteroids are commonly prescribed earlier but a Cochrane review found limited evidence and no benefit (11).

Other non pharmacological treatments for PHN include the following:

- Acupuncture
- Relaxation technique
- Heat therapy
- Cold therapy
- Transcutaneous electrical nerve stimulation (TENS) (12)
- Spinal cord stimulator (13)
- In May 2006 the Advisory Committee on Immunization Practice approved a vaccine against shingles (Zostavax). It is a potent version of chicken pox vaccine and evidence shows that it reduce the incidence of PHN (14). The CDC recommends use of this vaccine in all persons over 60 years old (15).

Trial with pregabalin versus amitriptyline for about 2 month noticed that pregabalin is better than amitriptyline (16). Some trials demonstrated that combination therapy is more efficacious than either the drugs as monotherapy (17,18).

As more than one mechanism of action present in PHN, many patients respond to therapy in different way. Some patients improved complain with the duration of the disease. The main aim of our study was to assess the clinical efficacy with amitriptyline and pre gabalin for the period of 6 months.

Methods

An open ended randomized comparative study of clinical efficacy with amitriptyline and pregabalin was carried out in Midnapore Medical College Skin OPD during the period of April 2008 to December 2009. Patients were included for the study with following the inclusion criteria: (1) PHN of more than 1 month duration (ii) pain atleast moderately severe, (iii) patients ≥40 yrs. Some patients excluded from the study if they have history of cardiac disease, seizure disorder, severe depression with suicidal tendency, another significant pain problem and previous history of brain damage caused by head injury or stroke.

All together 50 patients were included for the study. They are divided into two groups randomly: one group will receive 25 mg amitriptyline at night and another group pregabalin 75 mg twice daily (noon and night). Two medicines were allocated with every odd member for amitriptyline and even number for pregabalin. Patients were not allowed to take any analgesic during the study period. A written informed consent was obtained from each patient during the enrolment. General physical, neurological and other systemic examinations were done prior to enrollment. Institutional ethic committee cleared the study protocol.

Total period of study was 6 months and the patients were reviewed on 2 months, 4 months and 6 months, respectively. Initial dose of amitriptyline was 10 mg at night which increased to 25 mg OD at night at 5th day. Initial dose of pregabaline was 75 mg once daily and increased to 75 mg twice daily after 5 day.

A visual analogue scale (VAS) was used to evaluate the pain. The categorical scale used the words as:

1. No pain,

2. Mild – present but not bothering once,

3. Moderate – bothersome, disagreeable and unpleasant,

4. Severe – unbearable and

5. Very severe – requiring bed rest.

Improvement of categorical scale was a change from moderate or severe to lesser category. Relief of pain was assessed by percentage rating, with patient being asked to estimate from 0 to 100%, how much better it was. We considered 80%, 90%and 100%improvement in 2 month, 4 month and 6 month respectively as satisfactory improvement. A check list of side effects was recorded in each visit and if some side effect was present, the patients were asked whether it was tolerable or intolerable.

Statistical Analysis

Comparisons of clinical efficacy between the two groups were compared using mantel-Haenszel chi-square test. Odds ratio and 95% confidence intervals was calculated by standard methods. All statistical analyses were performed using MedCalc statistical software (version 11.4, MedCalc Software). The level of statistical significance was set at p value less than 0.05.

Results

All together 50 patients were included for the study. They were divided into two groups: amitriptyline (n = 25) and pregabalin (n = 25). Most of the patients completed the total 6 months study period. Some of the patient stopped treatment due to low or no effect of improvement with the medicine. We have received the information about their reason to stop medicine by telephone interview. Out of total 50 patients, male were 32 (64%) and female were 18 (36%) (Table 1).

According to distribution of the herpes zoster lesion, we have seen 4 types of HZ. Among these distribution thoracic was commonest 54% (27/50). Other types were trigeminal 16% (8/50), cervical 24% (12/50) and lumber 6% (3/50). We found sixty six percent patients with presence of prodromal symptoms.

At the end of 2 months, more than 80% improvement of pain perception was considered as satisfactory improvement (Table 2). Statistically significant improvement of pain perception was noticed in pregabalin group of patient (Chi-square=5.5967, p=0.0179). Satisfactory improvement

Table 1. Characteristics of the studied sample

Characteristics	Treatment		Inference
	Pregabalin	Amitriptyline	
Age (years), mean (95% CI)	55.4 (51.6-59.2)	54.4 (50.6-58.2)	p>0.05
Gender			
Male	16 (64.0%)	16 (64.0%)	p >0.05
Female	9 (36.0%)	9 (36.0%)	
Place of occurrence			
Thoracic	10 (40.0%)	17 (68.0%)	p>0.05
Trigeminal	6 (24.0%)	2 (8.0%)	
Cervical	7 (28.0%)	5 (20.0%)	
Lumbar	2 (8.0%)	1 (4.0%)	
Prodromal symptom			
Present	15 (60.0%)	18 (72.0%)	p>0.05
Absent	10 (40.0%)	7 (28.0%)	
PHN severity			
3	20 (80.0%)	23 (92.0%)	p>0.05
4	5 (20.0%)	2 (8.0%)	
Severity of pain			
3	3 (12.0%)	4 (16.0%)	p>0.05
4	18 (72%)	19 (76.0%)	
5	4 (16.0)	2 (8.0%)	

was found in 36% of pregabalin patient compare to 8% of amitriptyline patients. In pregabalin group, the rate of improvement was more than 6 folds higher (OR=6.46; 95% CI: 1.23-34.01) of that found in amitriptyline group.

At the end of 4 months, 90% improvement of pains perception was considered the satisfactory improvement. Here we noticed that 61.91% of pregabalin group patient observed the significant satisfactory improvement versus 27.78%with amitripyline group (Table 3). Satisfactory improvement in patients with pregabalin group was significantly 4 times higher than patients with amitripyline group (OR=4.23, 95% CI: 1.09-16.40, z-statistic=2.082, p<0.05).

At the end of the study i.e. 6 months, we considered the 100%improvement as satisfactory progress (Table 4). According to the VAS score, satisfactory improvement was 89%(OR=1.89, 95% CI: 0.53-6.69) higher in pregabalin group than amiripyline group (52.38% vs 36.84%, p>0.05) However, the comparative results were not statistically significant.

We found the adverse effects of the drug mainly during the early phase i.e. 2 months. Dryness of the month was the commonest side effect with amitriptyline group and dizziness in pregabalin group. More importantly, rate of side effects was 1.6 times higher in amitripyline group than pregabalin side effect (OR=1.64; 95% CI: 0.46-5.97). The intensity of adverse reaction was mild to moderate and more of the patient discontinued due to adverse reaction and majority was found in amitripyline group.

Discussion

The present study demonstrated that pregabalin to be more efficacious compare to amitriptyline in relieving the pain perception at the end of 2 months and 4 months treatment and the results were statistically significant. But there was no statistically significant difference in terms of satisfactory improvement in either group after 6 months though some better improvement noticed in pregabalin compare to amitriptyline. A Study suggested that long term treatment with pregabalin may be beneficial in patient with pregabalin (19). Various study with amitriptyline, nortriptyline or desepramine versus placebo showed significant benefits associated with antidepressant therapy (20,21). Pregabalin used in a multicentre, parallel group, double blind placebo controlled 8 weeks randomized clinical trial noticed significant reduction of post herpetic pain (22).

There were many publication with comparative study of clinical efficacy demonstrate one drug versus another drug. A randomized, double blind, cross over study with amitriptyline versus maprotyline was published in 1992 and the results showed that amitriptyline was better than maprotyline though statistically insignificance (23). In another study demonstrated that amitriptyline and nortriptyline were equally effective with approximately 50% achieving good response (24). Another one comparative study demonstrated with gabapentine and nortriptyline that both the drugs almost equally effective but gabapentine better tolerable (25). Comparative study with gabapentine versus pregabaline noticed better pain improvement with pregabalin which was about 6 times that of gabapentine in terms of effective in dose conversion (26). Another two studies published in 2009 and 2010 found that combination therapy with two different drugs were better than the either drugs. Combined therapy with gabapentine and nortriptyline was more effective that either drug giving alone in neuropathic pain (17). Combination therapy with amitriptyline and pregabalin were better to relieve pain perception in post herpetic neuralgia patient compare to the either drugs (18).

Table 2. Comparative assessment of PHN after 2 months of initiation of therapy

Treatment	80% improvement	<80% improvement	Total
Amitriptyline	2 (8%)	23 (92%)	25
Pregabalin	9 (36%)	16 (64%)	25
Chi-square= 5.597, df=1, p=0.0179			

Table 3. Comparative assessment of PHN after 4 months of initiation of therapy

Treatment	90% improvement	<90% improvement	Total
Amitriptyline	5 (27.78%)	13 (72.22%)	18
Pregabalin	13 (61.91%)	8 (38.09%)	21
Chi-square= 4.426, df=1, p=0.0354			

Table 4. Comparative assessment of PHN after 6 months of initiation of therapy

Treatment	100% improvement	<100 improvement	Total
Amitriptyline	7 (36.84%)	12 (63.16%)	19
Pregabalin	11 (52.38%)	10 (47.62%)	21
Chi-square= 0.447, df=1, p=0.504.			

Conclusion

Though earlier study demonstrated that pregabalin is better than amitriptyline in 2 month study period but after the 6 months of study period did not find any significant difference between the two groups. As the sample size is small, it is very difficult to comment the definite conclusion.

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