Original Article

The Effect of Pregabalin and Metformin on Subacute and Chronic Radiculopathy

Behnaz Ansari, Majid Ghasemi, Mana Ahmadian, Fariborz Khorvash

From the Department of Neurology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Radicular pain is one of the most common forms of chronic pain in the world, which has challenges about effective medical therapy. The aim of this study was to evaluate the effect of pregabalin (PGB) and metformin (Met) on subacute and chronic radiculopathy. **Materials and Methods:** This double-blind prospective clinical trial was performed on 71 patients with subacute and chronic cervical and lumbosacral radiculopathy. Group A was treated with PGB 75 mg daily while Group B was treated with PGB 75 mg daily and Met 500 mg daily for 3 months. Finally, the pain score in both groups was evaluated based on visual analog scale (VAS) and numerical scale pain. **Results:** The results showed a significant reduction in VAS and pain severity in both groups but this reduction in the terms of VAS (47.79% vs. 46.48%, $P = 0.125$) and pain severity (47.1% vs. 39.2%, $P = 0.264$) was more in treated patients with PGB and Met as compared to PGB group while total pain experience (53.5% vs. 49.1%, $P = 0.464$) and interference with daily function (57.1% vs. 50.61%, $P = 0.726$) were more in patients treated with PGB alone. **Conclusion:** Our results showed that PGB and PGB + Met reduced pain intensity and interference with daily function while we did not observe significant differences between two groups. PGB alone would have the potentiality to become a simple and economic means to decrease radicular pain.

Keywords: *Metformin, pregabalin, radicular pain*

Introduction

Low back pain (LBP) is one of the most common musculoskeletal disorder which is experienced in approximately 80% of adults.[1] Disc degeneration is one of the main reasons of chronic LBP (39%), which causes both biochemical and mechanical disorder that poses radiculopathy, a disorder caused by nerve root compression.[2]

Radicular pain challenging in treatment with existing therapeutic choices.[3] Many drugs are prescribed as treatment including nonsteroidal anti-inflammatory drugs, opiates, anticonvulsants, antidepressants, benzodiazepines, corticosteroids, muscle relaxants, and transdermal anesthetics, but few have been shown to be effective.[4] Subacute or chronic radicular pain can negatively affect patient's quality of life and ability to function his/her routine life. With appropriate treatment just one-fourth of patients with radicular pain receive a 50% relief from pain.[5]

Pregabalin (PGB) is a structural analog of gamma-aminobutyric acid that selectively binds to alpha2-delta subunit of voltage-dependent calcium channels and poses analgesic, anxiolytic, and antiepileptic effects.[6] In some studies, PGB has shown to have positive effects on pain relief and improving the component of pain and sleep disturbances in patients with peripheral diabetic neuropathy,[7,8] postherpetic neuralgia,[9] and spinal cord injury as a model of central neuropathic pain.[10]

Furthermore, metformin (Met) has been used widely as an antidiabetic drug.[11] Although the mechanism of Met action is not well clear, it has been recently suggested that Met has some pleiotropic actions, especially by affecting AMP-activated protein kinase (AMPK).[12] Several roles of AMPK have been presented in diabetes mellitus, neuroprotection, anti-inflammation, and alteration of oxidative stress.[13,14] Possibility of injury-induced neuropathic pain inhibition has been indicated for AMPK.[13] Moreover, in a study of Taylor *et al*., Met use was associated with a decrease in lumbar radicular pain.[15]

There is no information about comparison of PGB and Met in patients with radicular

How to cite this article: Ansari B, Ghasemi M, Ahmadian M, Khorvash F. The Effect of Pregabalin and Metformin on Subacute and Chronic Radiculopathy. Adv Biomed Res 2018;7:26.

Received: May, 2016, **Accepted:** October, 2016.

Address for correspondence:
Dr. Mana Ahmadian, Department of Neurology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: manaahmadian85@gmail.com

Access this article online

Website: www.advbiores.net

DOI: 10.4103/2277-9175.225599

Quick Response Code:

pain; therefore, this study was designed to evaluate effectiveness of PGB and Met on subacute and chronic radiculopathy.

Materials and Methods

Study design and target group

This double-blind prospective clinical trial was conducted in Neurology Department of Isfahan Alzahra and Kashani Hospitals, educational centers, from August 2014 to December 2015. The patients suffering from subacute (LBP for 4–8 weeks)[16] and chronic (LBP for >8 weeks)[16] cervical and lumbosacral radiculopathy receiving PGB (Group A) were compared to patients receiving PGB with Met (Group B). Inclusion criteria consisted of patients referred to Neurology Department of Alzahra and Kashani Hospitals with a diagnosis of subacute and chronic radiculopathy based on the international classification of diseases who has signed consent form to participate in the study and having age between 20 and 60 years. Exclusion criteria consisted of age <20 years or >60 years, dissatisfaction to continue participation in the study, improper use of drugs (PGB and Met), lose to follow-up due to various causes, comorbidity of diabetes and polyneuropathy, diabetic and other neuropathies, such as uremic, thyroid, liver, and B_1 deficiency, consuming drugs effecting neuropathy such as gabapentin and tricyclic antidepressants, clinical Red flags of tumor and infection, creatinine >2.5, that is, contraindication of Met consumption, incidence of blurred vision, clumsiness confusion, and drowsiness due to PGB consumption.

Participants

The study flowchart is shown in Figure 1. Eighty patients with diagnosis of subacute and chronic cervical and lumbosacral radiculopathy, who had been diagnosed by a neurologist and based on inclusion and exclusion criteria, were included in the study. Subacute and chronic cervical and lumbosacral radiculopathy were diagnosed with clinical signs and symptoms and results of electromyography/neural conducting velocity.

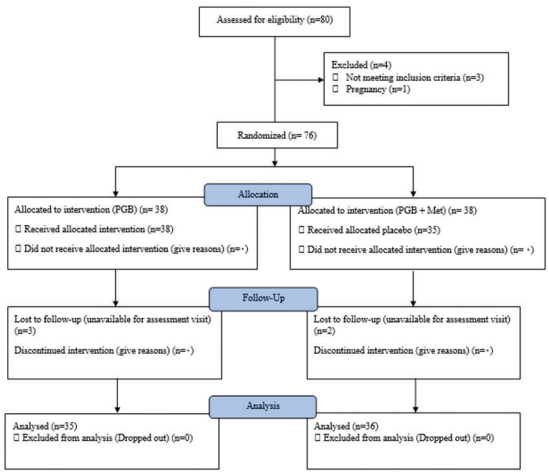

Figure 1: Study flowchart (CONSORT Format)

All eligible patients were randomly divided into two groups using a block randomization procedure with matched patients in each block based on age and sex. Before administration, pain intensity was measured using visual analog scale (VAS) and numerical scale pain (NSP) [Tables 1 and 2]. Group A was treated with PGB 75 mg daily (Abidi Corp.) while Group B were treated with PGB 75 mg daily (Abidi Corp.) and Met 500 mg daily (Aria Corp.) for 3 months.

The study received ethics approval from the Ethics Committee of Isfahan University of Medical Sciences, and

Table 1: Numerical scale pain for pain comparing at beginning and within 3 months

Pain scale	Score
Pain characteristics	None=0
Throbbing	Mild=1
Shooting	Moderate=2
Stabbing	Severe=3
Sharp	
Cramping	
Gnawing	
Hot/burning	
Aching	
Heavy	
Tender	
Splitting	
Tiring/exhausting	
Sickening	
Fearful	
Punishing	
Pain now	0-10
Total pain experience	None=0
	Mild=1
	Discomforting=2
	Distressing=3
	Horrible=4
	Excruciating=5
Interference with daily function	0-3=does not interfere
General activity	4-5=completely interfere
Mood	
Working ability	
Normal working routine	
Relations with other people	
Sleep	
Enjoyment of life	
Ability to concentrate	
Appetite	

all participants filled written informed consent. Finally, VAS and NSP [15] were measured after 3 months of intervention in both groups.

As Met reduces the level of Vitamin B_{12}, we checked serum levels of Vitamin B_{12} before and after intervention in Group B. If the serum levels of Vitamin B_{12} were lower than normal, we treat patients after intervention with folic acid.

Data analysis

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using IBM SPSS version 22, United States software. To compare qualitative variables, Chi-square test was used. Normal distribution of all studied parameters was checked with Kolmogorov–Smirnov test. Student's *t*-test and paired *t*-test were used for variables which were in a normal distribution, besides Mann–Whitney and Wilcoxon test were used for variables that were not in normal distribution. $P < 0.05$ was considered statistically significant.

Results

In this study, total number of 79 patients was participated in the study. Eight patients excluded due to incidence of PGB side effects such as drowsiness. Thirty-five patients were in PGB group and 36 were in PGB plus Met group. Demographic features in terms of age ($P = 0.781$), sex ($P = 0.737$), body mass index ($P = 0.667$), duration of pain ($P = 0.619$), pain characteristic ($P = 0.513$), and interference with daily function ($P = 0.169$) in both groups were similar. While VAS (6.8 vs. 5.4, $P < 0.001$), pain severity (2.76 vs. 2.5, $P = 0.048$), and total pain experience (3.36 vs. 2.71, $P < 0.001$) in patients treated with PGB and Met were significantly higher as compared to PGB group [Table 3].

As obtained, after 3-month intervention, VAS, pain severity, total pain experience, and interference with daily function were significantly decreased in both groups ($P < 0.001$) [Tables 4 and 5]; however, we did not observe significant differences between the groups [Table 6]. Moreover, by analyzing mean changing score in terms of VAS, pain severity, total pain experience, and interference with daily function, no significant differences were observed between groups. However, reduction rate in these subunits in both groups was significant but this reduction in terms of VAS (47.79% vs. 46.48%) and pain severity (47.1% vs. 39.2%) was more in patients treated with PGB and Met as compared to PGB group while reduction in total pain experience (53.5% vs. 49.1%) and interference with daily function (57.1% vs. 50.61%) was more in patients treated with PGB alone; however, these differences were not statistically significant.

Discussion

The results of the present study about mean changing score in terms of VAS, pain severity, total pain experience, and interference with daily function, have not shown significant differences between patients receiving PGB and PGB with Met. However, reduction rate in these subunits in both groups was significant but this reduction in terms of VAS (47.79% vs. 46.48%) and pain severity (47.1% vs. 39.2%) was more in patients treated with PGB and Met as compared

Table 2: Visual analog scale for pain comparing at beginning and within 3 months

Score	Duration	Score	Intensity	Score	Frequency
4	>15 min	1	Once at night	2	Three times a week
2	Between 5 and 15 min	2	More than once at night	3	Most nights
1	<5 min			4	Every night

Table 3: Studied variables before intervention in both PGB and PGB with Met groups

Group variables	PGB	PGB+Met	*P*
Age (year)	41.42±11.86	42.25±12.9	0.781
Sex (Male) (%)	23 (65.7)	25 (69.4)	0.737
BMI (kg/m^2)	30.02±5.4	29.5±4.9	0.667
Duration of pain (years)	8.14±2.84	8.44±2.22	0.619
VAS	5.4±1.53	6.8±1.58	<0.001
Pain characteristic			
Throbbing (%)	1 (3.2)	0	0.513
Shooting (%)	6 (19.4)	6 (19.4)	
Stabbing (%)	1 (3.2)	4 (12.9)	
Sharp (%)	0	1 (3.2)	
Cramping (%)	20 (64.5)	17 (54.8)	
Hot/burning (%)	0	1 (3.2)	
Aching (%)	3 (9.7)	2 (6.5)	
Pain severity in NSP	2.5±0.65	2.76±0.42	0.048
Total pain experience in NSP	2.71±0.75	3.36±0.68	<0.001
Interference with daily function in NSP	3.8±0.86	4.05±0.67	0.169

Table 4: Mean differences in studied variables in PGB group

Variables	Mean	SD	95% confidence interval of the difference		*t*	df	Sig
			Lower	Upper			
VAS	2.51	1.66	1.94	3.08	8.911	34	<0.001
Pain severity in NSP	0.98	1.44	0.48	1.48	4.029	34	<0.001
Total pain experience in NSP	1.45	1.01	1.11	1.8	8.535	34	<0.001
Interference with daily function in NSP	2.17	1.31	1.71	2.62	9.754	34	<0.001

Table 5: Mean differences in studied variables in PGB with Met group

Variables	Mean	SD	95% confidence interval of the difference		*t*	df	Sig
			Lower	Upper			
VAS	3.25	2.27	2.48	4.01	8.581	35	<0.001
Pain severity in NSP	1.3	0.88	1	1.6	8.815	35	<0.001
Total pain experience in NSP	1.65	1.21	1.24	2.06	8.143	35	<0.001
Interference with daily function in NSP	2.05	1.45	1.56	2.54	8.488	35	<0.001

Table 6: Studied variables 3 months after intervention in both PGB and PGB with Met groups

Group variables	PGB	PGB+Met	*P*
VAS	2.88±1.72	3.55±2.13	0.151
Pain severity in NSP	1.51±1.76	1.45±0.78	0.863
Total pain experience in NSP	1.25±0.81	1.7±1.23	0.073
Interference with daily function in NSP	1.62±1.33	2±1.43	0.262

to PGB group while total pain experience (53.5% vs. 49.1%) and interference with daily function (57.1% vs. 50.61%) were more in patients treated with PGB alone.

There are few trials which have assessed pharmacological management of subacute and chronic radiculopathy. Our data appear to be the first in which PGB with Met has been used for the management of cervical and lumbosacral radiculopathy. Our findings suggest that both PGB alone and PGB with Met can be effective in decreasing radicular symptoms and pain, patient disability, and improvement of patient's quality of life.

Monotherapy with PGB, or as an add-on therapy such as Met, caused a very marked decrease in pain (over 50%). The proportion of responders in this study, 46.48% and 47.79% in monotherapy (PGB) and add-on (PGB + Met) groups, respectively, was at least similar to study which administrated PGB only among patients with diabetic neuropathy (39 and 48%),[7,8] postherpetic neuralgia (28 and 75%),[17,18] and patients with central neuropathic pain associated with spinal cord injury (22%).[19]

Moreover, we found improvement in interference with daily function in both groups, but a little more in PGB group. Due to frequent co-occurrence of sleep disturbances, enjoyment, concentration, and mood decrease in such patients,[20] PGB may have positive role in such situations.

Adding Met did not decrease pain severity based on VAS and NSP. As observed, PGB alone had the same effect in decreasing pain intensity. However, many studies showed similar results, Taylor *et al*. presented that Met therapy is associated with a decrease in severity of lumbar radicular pain.[15]

Moreover, our results are in accordance with some other mechanistic studies from preclinical models which have demonstrated a powerful antihyperalgesic/antiallodynic effect of Met and other AMPK activators on chronic pain[21,22] and a recent case report suggesting efficacy of Met in humans.[23]

These differences between our results and mentioned studies may be due to different sample size, demographic features of studied population, the dosage of Met, and excluding diabetic patients, which did not perform in mentioned studies. Consequently, our results are more close to reality by eliminating diabetic patients.

Conclusion

Our results showed that both PGB alone and PGB + Met reduced pain intensity and interference with daily function while we did not observe significant differences between two groups. PGB alone would have the potentiality to become a simple and economic means to decrease radicular pain. A large-scale study is needed to come to clinical guidelines and recommendation for neurologist and neurosurgeries.

Acknowledgment

We gratefully acknowledge the dedicated efforts of the investigators, coordinators, volunteer patients who participated in this study, and the Clinical Research Development Units of Isfahan Alzahra Hospital.

Financial support and sponsorship

This study was financially supported by Vice-Chancellor for research and technology of Isfahan University of Medical Sciences (Grant number: 394639).

Conflicts of interest

There are no conflicts of interest.

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