Comparison of Gabapentin Monotherapy vs. Combination Therapy of Methyl Cobalamin and Gabapentin in Treating Diabetic Neuropathic Pain

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Abstract

Introduction: To evaluate effectiveness of gabapentin alone and combination therapy of gabapentin with methyl cobalamin with regards to decrease in pain in patients suffering from diabetic neuropathy.

Method: Patients studied constituted either gender with age ranging above 18 year up to 80 years. Patients suffering from diabetic neuropathy were followed in this study. They had painful neuropathic condition and were following treatment for controlling diabetes mellitus. They were divided into two groups (1 and 2) according to the type of drug used for the purpose of neuropathic pain. Group 1 patients received Gabapentin monotherapy while Group 2 patients received combined therapy of gabapentin and Methylcobalamin. Variables such as age, gender, weight, BMI, type of drug used and pain score were noted in proformas and data was then analysed with SPSS (VERSION 16).

Results: There were two groups of patients. One hundred fifty patients were receiving gabapentin (group 1). While other 150 subjects were put on the combination regimen of Gabapentin and Methyl cobalamine (group 2). On comparison of scores for pain between the two groups there was significant difference of pain decrease in the combination therapy group 2 as compared to the solo drug usage (gabapentin) in group 1. No adverse side effects of much significance were noted.

Conclusion: It is inferred from this study that combined therapy with Gabapentin and Methylcobalamin can be more efficacious as compared to treatment with gabapentin alone. This combination is safe with minimal side effects.

Keywords: Gabapentin • Methyl cobalamine • Combined therapy • Diabetes neuropathy • Pain control

Introduction

Diabetes Mellitus is also known as the pandemic of current modern times. The reason being ascribed to rapidly declining lifestyle [1-3]. Diabetes mellitus is spreading like a fire continuously giving rise to higher incidence rates worldwide. They are crossing the figure of 430 million adults approximately globally. Having said that its worldwide prevalence is expected to be near to 9% Diabetes Mellitus is not a name of mere single disease but a panadora box that expedite a number of complications comprising of vascular complications (Stroke, Myocardial infarction, peripheral vascular ailments [3,4]. Apart from these major complications there are also microvascular complications including diabetic retinopathy, diabetic Nephropathy, and peripheral neuropathy [4]. As these complications worsen in intensity they give rise to significant deterioration in quality of life of these patients [5].

Diabetic neuropathy is a painful and disabling condition that has huge incurring costs in terms of disturbed quality of life and financial burden while treating its complications. Its incidence is increasing as a consequence of poor treatment compliance and so faulty glycaemic control [6]. According to one estimate every third diabetic patient suffers from diabetic neuropathy [7].Its prevalence is different in various countries owing to heterogeneity of population and other factors such as heathcare systems, economical dynamics and social awareness [7].A UK study reported prevalence of painful diabetic neuropathy around 21% [6]. However, it is different in different countries depending upon the strictness of glycemic control [7,8].

Diabetic neuropathy (a painful condition) manifests as hike in symptoms at night. It has wide spectrum of symptoms such as sensation of needles, pins and burning sensations, sometimes electric or stabbing sensations. These may be intermittent or continuous. Stimuli of intensity as little as a touch of dressing (clothing) induce agonizing pain. This pain at night lead to disturbed sleep, resultantly affecting day time activities. This has negative impact on the office or work place efficiency and their social life. In extreme scenarios, there can be also being loss of appetite leading to diabetic neuropathic cachexia [8].

Management of diabetic neuropathic pain includes tight glycemic control and alleviation of symptomatic pain. Over course of time, utilization of antidepressants (amitriptyline or duloxetine), other drugs such as gabapentin and pregabalinhave been in use. Opiods have also been tried in this condition. And others topical agents such as capsaicin are also under trial [8-11].

Combination of methylcobalamin, Gabapentin is used in Pakistan. However, their comparison with regards to efficacy with gabapentin alone in treatment of diabetic painful diabetic neuropathy has not been studied much.

Materials and Methods

It was a descriptive observational study done at Army medical college and affiliated hospitals and health facilities conducted over time duration of 1 year. Three hundred patients were included in the study using a nonprobability consecutive sampling technique. Patient's age ranged between 18 and 80 years. They were on diabetic control regimen (Oral medications/Insulin or combination of both). Patients included in study had HbA1c maintained at 8% or lower values.

Exclusion criteria comprised of those suffering from chronic liver ailments or renal insufficiency, patients who were Pregnant or baby feeding mothers, those suffering at same time from some degree of peripheral vascular disease. Patients who had prior history of therapy with

Table 1. Demographic variables of the two groups.

Variables	Group 1 (Gabapentin alone therapy)	Group 2 (Combined therapy)	p-Value
Age	48.11 ± 10.69 years	47.35 ± 11.37 years	0.08
Male	87	77	0.09
Female	63	73	0.10
Body Mass Index(BMI)	28.31 ± 5.12	29.43 ± 4.87	0.11
Mean values of HbA1C	7.71 ± 0.91	7.93 ± 0.84	0.09
Insulin use	21(14%)	19(12.6%)	0.13
Oral hypoglycemic	71(47.3%)	86(57.3%)	0.11
Combined insulin and oral therapy	58(38.6%)	45(30%)	0.09

Table 2. Decrease in pain inside each group (intragroup comparison).

Group studied	Pain at initial visit	Pain at three months	p-Value (paired t-test)
Group 1 (Gabapentin therapy)	7.61 ± 3.7	4.91 ± 1.29	0.44
Group 2 (Combined therapy)	7.59 ± 2.98	3.71 ± 1.14	0.02

Table 3. Decrease in pain compared between the two groups(inter group comparison).

Pain score	Group 1 (Gabapentin therapy)	Group 2 (Combined therapy)	p-value (independent t-test)
At initial visit	7.61 ± 3.7	7.59 ± 2.98	0.99
At 1 month	6.8 ± 2.87	6.3 ± 3.11	0.90
At 3 months	4.91 ± 1.29	3.71 ± 1.14	0.03

gabapentin and pregabalin or in case they had other neurologic disorders not directly related to diabetic neuropathy were excluded. Patients were counselled regarding follow up and informed consent taken for inclusion in the study. Patients were given different kinds of pain control medication regimen according to physician choice and were divided into into two groups (1 and 2) accordingly. Diabetic mellitus control was tailored for each individual according suitability to their situation and achievement of the target sugar controls.

Group 1 was given Gabapentin alone while Group 2 was administered combination therapy of methylcobalamin and gabapentin. Patients were taught about the importance of compliance to both pain medication and the sugar control. At start of inclusion into study each patient underwent assessment for computing baseline pain score utilizing tool of visual analogue pain score. Patients were called to Outdoor clinic on monthly basis till next three months after starting the pain control regimen. At each visit they were assessed for pain score using visual analogue pain score.

Diabetes Mellitus was labeled as fasting blood sugar levels exceeding cut off value of 126 mg/dl or if the postprandial blood sugar (at 2 hours) was exceeding 200 mg/dl as computed on two different timings while patients were on treatment for diabetes. Different variables were recorded in the proforma for each patient at the time of follow up interviews regarding their overall pain control, included gender, BMI, age, HbA1C status at induction of start of treatment, pain at baseline and then at follow up visit after commencing the pain treatment.

After proforma filling the data was transferred into SPSS (SPSS version 16).For describing continuous variables Mean and standard deviation values were utilized (such as Age, pain score).For depicting categorical variables frequency/percentages were computed (such as gender). To compare efficacy among these groups chi square test was applied. The p-value of less than 0.05 was labelled as a statistically significant value. Paired sample t test was applied to see efficacy of treatment in group 1 and group 2. p value of less than 0.05 was taken as significant. While student test was used to see difference between the two groups.

Results

Overall 371 patients were screened to be included in study and at the end 300 patients eligible for study were included keeping in view the inclusion exclusion criteria. One hundred fifty patients were receiving gabapentin (group 1).While other 150 subjects were put on the combination regimen of Gabapentin and Methylcobalamin (group 2). Various demographic factors in both groups were alike on the whole (Table 1). The mean HbA1C (%) were alike in two groups.

On first visit in outdoor clinic the baseline scores for pain were recorded to be 7.73 ± 3.27 (on scale of Visual Analog Pain Score and 4.35 ± 1.39 after 3 months of treatment (p-Value 0.01). The patients in group 1 had a pain score of 7.61 ± 3.7 and 4.91 ± 1.29 at initial visit and 3 months follow up respectively. While for group 2 (combination therapy of gabapentin and Methylcobalamin) the pain scores were 7.59 ± 2.98 and 3.71 ± 1.14 at initial visit and 3 months follow up respectively (Table 2).

On comparison of scores for pain between the two groups applying student t test ,it was found that there was significant difference of pain decrease in the combination therapy group 2 as compared to the solo drug usage (gabapentin) in group 1 (Table 3). No adverse side effects of much significance were noted during the follow up period. Minor side effects of dizziness and mild allergic skin reactions were seen in approximately 11% patients.

Discussion

Painful diabetic neuropathy is a debilitating condition complicating almost more than 22% of subjects suffering from diabetes mellitus [9-11]. Wide range of treatment regimens and drugs are present in market for diabetic neuropathic pain such as Tricyclic antidepressants, SSRIs, Gabapentin, Pregabalin, other antiepileptic drugs and few topical medications for use. Till present time no specific treatment regimen has been agreed upon and as such no single drug therapy can be labelled as the most efficacious one. In such an evolving scenario combination of several drugs therapy is thought to prove to be more effective [11]. Various studies have been tried in recent past. However there is paucity of such studies especially in subcontinent [12].

Diabetic neuropathy is a sensorimotor neuropathic phenomenon marked by paranesthesia, pain and some degree of sensory loss. This condition generally afflicts diabetic patients disturbing significantly their health condition and the consequential quality of life. They experience difficulty in doing daily life chores and office work due to pain and impinging on quality their sleep [13]. On Pathophysiological level there is oxidative stress, polyol pathway flux,some glycation end products and activation of protein kinase C, all come up with microvascular derangements and nerve physiology getting dysfunctioned [14,15]. Thus, all these pathophysiological factors emanates from the disrupted biochemical activities. These ultimately lead to alterations at cellular physiology such as cellular transport mechanisms, changes in endoskeletal structure, depletion of neurotropinsresulting in nerve ischemia.

As mentioned before, few drugs have been tried regarding neuropathic pain. Opioids are one of these drugs that have been tested for utilization in symptomatic amelioration of neuropathic pain in diabetic patients. However, it is to be noted that they only furnish symptomatic relief, and as such has nothing to do much at the pathophysiological level of all the processes discussed above. Moreover opioids also result in higher incidence of unfavorable side effects events [16]. Clinical trials to take into account these physiological processes at cellular levels need further enhancement. Pregabalin has also been tried in the treatment of diabetic peripheral neuropathy, it is said that even though it might alleviate the

pain, it can't help in decreasing the load of the oxidative stress. Alpha lipoic acid has also proved some promising results and hopes to be used as a drug for coping with the neuropathic pain [17].

According to one study significant decrease in neuropathic pain was observed in diabetic patients who were put on regimen of vitamin B12 in comparison to patients who were utilisingnortriptyline [18].In yet another study it was found that oral Gabapentin proved to bring promising results for the management of neuropathic pain secondary to diabetes mellitus. Furthermore they observed adequate pain control. In addition to this, Gabapentin usage had an added advantage of inducing low rates of side effects thus proving it to be a safe drug [19]. In our study, on first visit in outdoor clinic the baseline scores for pain were recorded to be 7.73 ± 3.27 that decreased to 4.35 ± 1.39 after 3 months of treatment. The patients in group 1 had a pain score of 7.61 ± 3.7 and 4.91 ± 1.29 at initial visit and 3 months follow up respectively. While for group 2 (combination therapy of gabapentin and Methylcobalamin) the pain scores were 7.59 ± 2.98 and 3.71 ± 1.14 at initial visit and 3 months follow up respectively (Table 2).

A study showed that utilization of Gabapentin was efficacious in the treatment of painful condition of diabetic neuropathy. However they do commented that mild adverse events secondary to drugs side effects were noted. However Gabapentin usage resulted in quicker relief of pain symptoms [20]. Another study regarding evaluation of monotherapy with methyl cobalamin in patients with neuropathic symptoms didn't bring much fruitful results. However if methyl cobalamin is used in combination therapy with other drugs, can bring more favourable results regarding pain alleviation in diabetic neuropathy [21,22]. One study demonstrated superiority of using methyl cobalamin in injectable forms over placebo treatment. Their results manifested marked improvement in pain scores in the patients who were subjected to methyl cobalamin treatment as compared to those with placebo treatment [23]. In our study, there was significant difference regarding pain decrease in the combination therapy (group 2) as compared to the solo drug usage (gabapentin in group 1).No adverse side effects of much significance were noted during the follow up period. Minor side effects of dizziness and mild allergic skin reactions were seen in approximately 11% patients.

It was evident from the results that combined regimen therapy of gabapentin and methylcobalamin was more effective in ameliorating the pain in patients suffering from diabetic neuropathy. This study has some strength as it has a good sample number and done across 2 hospitals. However randomization was not done so we need more multicenter randomized controlled studies in future. We need some studies regarding effect on quality of life in terms of detailed questionnaires too.

Conclusion

This study manifested that combined therapy with Gabapentin and Methylcobalamin is more effective as compared to monotherapy with gabapentin. Furthermore, this combination is safe with minimal side effects and as such tolerated well by the patients.

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