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COMPARATIVE STUDY OF EFFICACY AND SAFETY OF GABAPENTIN AND AMITRIPTYLINE MONOTHERAPY IN PATIENTS OF PAINFUL DIABETIC NEUROPATHY

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ABSTRACT The objective of this study was to compare the efficacy and safety of gabapentin and amitriptyline monotherapy in painful diabetic neuropathy. This was a 12 weeks, observational, open label, comparative, multiple followup study. A total of 110 patients were included in the study with 55 patients receiving gabapentin and 55 patients receiving amitriptyline. Treatment was provided for a period of 12 weeks and patients was called for follow up at 4, 8 and at 12 weeks (3 follow ups). Baseline assessment was done by Biochemical tests consisting of CBC, serum creatinine, serum Urea, liver function tests, HbA1c. At the time of follow up patient were be evaluated for efficacy, safety and tolerability. Results were comparable with no significant statistical difference. Monotherapy with gabapentin and amitriptyline produced a clinically and subjectively meaningful pain relief in patients with diabetic painful neuropathy with onset of pain relief being fast.

KEYWORDS : Gabapentin, Amitriptyline, Diabetic Neuropathy

INTRODUCTION

The prevalence of diabetes globally was estimated to be 9% in adults in 2014.[1] Diabetes is a chronic disease that starts either when the pancreas is not producing enough insulin or when the body cannot utilize the insulin. Insulin is a hormone that regulates blood sugar.[2] The diabetes prevalence is increasing at an alarming rate.[3-6] From 1974 to 1994, the prevalence of diabetes increased from 8.9% to 12.3% in the world.[7] Diabetes Mellitus (DM) has been known to physicians since ancient times. Initially, the disease was described as Diabetes (Greek-*syphon*) literally meaning passing huge amounts of water, by the Greek physician *Aretaeus*. Thomas Willis, an English physician added Mellitus (Latin- *honey)*, to signify 'sweet urine' passed by these patients. By 2025 the prevalence of DM will increase to 300 million patient's worldwide.[8]The prevalence of diabetes, and especially of type 2 diabetes (T2DM), is increasing at an alarming rate. According to the update by the International Diabetes Federation (IDF) more than 415 million adults aged 20–79 years have diabetes in 2015 which is projected to increase 642 million by 2035.[9]

Currently there are more people with diabetes in urban (269.7 million) rather than in rural (145.1 million) areas. In low and middle income countries, the number of people diagnosed with diabetes in urban areas is 186.2 million while it is 126.7 million in rural areas. By 2040, globally it is expected to widen, with 477.9 million people living in urban areas and 163.9 million in rural areas.[9] In addition, there are 415 million adults who are presently estimated to have diabetes; there are 318 million adults with impaired glucose tolerance, which puts them at high risk of diabetes development in future. The prevalence is increasing in every country, and major economic, healthcare impact will be seen in developing countries, as these countries are home to as much as 80% of people with diabetes.[10] Diabetic neuropathy is defined as "presence of signs or symptoms of peripheral nerve damage in people with diabetes after excluding other causes"[11]. Acute sensory neuropathy is an uncommon syndrome associated with periods of poorly controlled diabetes, as well as sudden improvements in glycemic control (so called "insulin neuritis"). It is characterized by acute or sub-acute onset of severe painful symptoms, in glove and stocking distribution, usually with nocturnal exacerbation.[12] Diabetic autonomic neuropathy (DAN) is a grave complication of diabetes and carries up to a five-fold increased risk of mortality.[13]

MATERIALS AND METHODS

The present study entitled "Comparative Study of Efficacy and Safety of Gabapentin and Amitriptyline monotherapy in Patients of painful diabetic neuropathy" was an institutional/ hospital based study conducted in Bhopal, the capital of Madhya Pradesh (MP), at Gandhi Medical College and associated Hamidia Hospital. This study was initiated after submitting the protocol and obtaining the approval of Institutional Review Board (IRB). It is an observational, open labeled, comparative, and multiple follow up study. This study was conducted for a period of 1 year duration. Case collection was done during first 6 months of the study. Last 6 months were reserved for follow up, analysis and integration of the collected data and interpretation of results. Inclusion criteria were a) Age 18 to 70 years ,b) Gender both male and female, c) Patients with type 2 DM, who are experiencing painful diabetic neuropathy for more than 3 months duration. The patients with type 2 DM and clinically relevant lower and upper limb polyneuropathy with significant pain and paresthesias lasting at least 3 months were enrolled in the study, after being diagnosed by the consultant neurologist and after obtaining an informed consent from the patient and applying the inclusion and exclusion criteria. Patients were analyzed on Short form McGill Pain questionnaires (SFMPQ) and Visual Analogue Scale (VAS). Paresthesia score (0-3) categorical scale (0-None; 1-Mild; 2-mild; 3-severe paresthesia), and Present Pain Intensity (0-5: 0-no Pain; 1-Mild Pain;2-Discomforting;3-Distressing;4-Horrible;5-Excruciating) from SFMPQ were evaluated. Patients were divided into two groups. Each group contained minimum of 55 patients. Group A consisted of patients who received oral tablet Gabapentin (GBP) and Group B consisted of patients who received oral tablet Amitriptyline (AMI). Treatment was provided for a period of 12 weeks and patients were called for follow up at 4, 8 and at 12 weeks (3 follow ups). Baseline assessment were done by Biochemical tests consisting of CBC, serum creatinine, serum Urea, liver function tests, HbA1c. At the time of follow up patient were evaluated for efficacy, safety and tolerability. Dose of gabapentin was 1800 mg per day (Divided in to 3 doses) and for Amitryptyline the dose was 30 mg H.S. per day. If neuropathic pain and SFMPQ score was not reduced then patient were excluded from the study and given further treatment for benefit of the patient. If subject was on some other medications for associated illnesses then doses of such drugs were kept constant during whole study period. Patients were enquired for the adverse events, if any, at each follow up and were documented and if required treatment will be given for the adverse drug reaction. Analysis of Data was performed using MS Excel and Graph Pad Prism.

Results

A total of 110 patients were included in the study out of which 55 patients were in group A receiving tablet Gabapentin and the rest 55 patients were in group B receiving tablet Amitriptyline. Majority of patients belongs to 41-50 yrs (39.1%) age group followed by 51-60 yrs (27.3 %). The mean age of patients in gabapentin group is 50.05 ± 9.97 yrs and mean age in amitriptyline group is 50 ± 10.14 yrs.

Both treatment groups were compared for the mean reduction in VAS score from baseline to 12th week. Both treatments were successful in decreasing the VAS score over the course of the study duration. Mean VAS score at baseline in Gabapentin group was 7.52 ± 0.99. This was comparable to Amitriptyline group in which VAS score at baseline was 7.58 ± 0.69, which was statistically not significant (p value - 0.73). These scores were different in comparison with the study done by Padmini et.al. [14] for the gabapentin treated group which showed 60.1 ± 17.5 on a 100 point VAS scale and Shankar et.al.[15] for the amitriptyline treated group which showed 7.1 ± 3.6 on a 10 point VAS scale.

There was significant decrease in the VAS score in both the groups from baseline at the end of the study period. After treatment, mean VAS score in Gabapentin treated group was reduced to 2.25 ± 0.52 (Table 1), our study shows a reduction of 71.82 % from baseline in gabapentin treated group. In the study done by Padmini et. al.[14] after treatment with gabapentin, the mean VAS reduction was 58.5%. The mean VAS score in amitriptyline group was reduced to 2.22 ± 0.82 which shows a reduction of 73.41 %. In the study done by Pratap Shankar et. al. [15] after treatment with amitriptyline, the mean VAS reduction was 49.4 %.

DURATION	GABAPENTIN GROUP	AMITRIPTYLINE GROUP	P VALUE
Baseline	7.52 ± 0.99*	7.58 ± 0.69*	0.73
12 weeks	2.25 ± 0.52*	2.22 ± 0.82*	0.79
P-value	< 0.0001	< 0.0001	

Table 1 - Comparison of VAS scores (*Mean ± Standard deviation)

The mean paresthesia score at baseline in Gabapentin group was 2.47 ± 0.50. There was significant statistical difference in Amitriptyline group in which mean paresthesia score was 2.76 ± 0.43 (Table 2). There was a significant reduction in Paresthesia score in both the groups from baseline at the end of 12 week period. After the treatment in gabapentin group, the mean paresthesia score was reduced to 0.54 ± 0.53 on 4 point categorical scale while in amitriptyline group the mean paresthesia score was reduced to 0.90 ± 0.68. These results were different in comparison with the study done by Dallocchio et.al [16] which showed that in gabapentin group, the mean final paresthesia score was 1.2 ± 0.8 while mean paresthesia score was 1.6 ± 0.7 in amitriptyline treated group.

DURATION	GABAPENTIN GROUP	AMITRIPTYLINE GROUP	P VALUE
Baseline	2.47 ± 0.50*	2.76 ± 0.43*	0.002
12 weeks	0.54 ± 0.53*	0.90 ± 0.68*	0.004
p-value	< 0.0001	< 0.0001	

Table 2 –comparison of Paresthesia scores (*Mean ± Standard deviation)

The result of the present study demonstrated that both Gabapentin and Amitriptyline are efficacious in the treatment of diabetes induced neuropathy and that, there is no statistically significant difference between the two treatment groups on the basis of mean reduction in VAS score, Paresthesia score.

In the present study, a total of 12 (21.82%) cases of adverse drug reaction were reported in Gabapentin treated group, while a total of 21 (38.18%) cases of adverse drug reaction were reported in amitriptyline treated group which were mild to moderate in intensity during the initial week of therapy and subsided after intervention or over the course of the study period. In the study done by Morello et al [17], a total of 17 (80.95%) patients in gabapentin treated group showed adverse drug reaction while 18 (85.71 %) in amitriptyline group showed adverse drug reaction.

A total of 101 patients completed the study out of which, 51 patients in Gabapentin group and 50 patients in amitriptyline group, completed the study. 4 patients in Gabapentin group and 5 patients in amitriptyline group were considered drop outs from the study, on the basis of the analysis set prior to study.

Results of this study demonstrated that patients treated with Gabapentin had a substantially lower rate of adverse drug reactions in relations to those treated with Amitriptyline. The above observation demonstrates that Gabapentin is well tolerated than Amitriptyline, however the difference between treatment groups regarding safety profile is statistically not significant (p value-0.09)

DISCUSSION

Both gabapentin and amitriptyline, in the dosages used in this study appear to provide an appropriate pain relief in diabetic neuropathic pain. Both of these used drugs had similar adverse effects, although considerable amount of pain is relieved in gabapentin group with DPN(Diabetic Peripheral Neuropathy) pain. It should be used as an alternative to patients in whom a less costly agent fails, for example amitriptyline. There have been a few limitations in our study e.g. a) This was an open label study, b) we were not able to include a placebo arm, c) the follow up of the patients was only for a period of 12 weeks and therefore long term efficacy and safety of the drugs could not be assessed.

The results from our analysis emphasize the need for conducting larger and longer duration multi-centric clinical trials and studies comparing the active treatments. It is proposed to use common pain measurement scales for evaluation of pain relief. Even though treatment guidelines for the management of peripheral neuropathy are available, it is suggested that treatment should be given by the physician, taking the patient's response into consideration.

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