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DRUG UTILIZATION PATTERN AND EFFICACY ANALYSIS OF DRUGS USED IN DIABETIC PERIPHERAL NEUROPATHY BY NERVE CONDUCTION STUDY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: Diabetic peripheral neuropathy (DPN) is the most common and distressing late complication of diabetes mellitus affecting nearly 50% of diabetic patients and treatment failure cases may develop foot ulcers and gangrene requiring amputation. DPN is responsible for 50% to 75% of non-traumatic amputations. Hence this study is aimed to assess the Drug utilization pattern in patients with DPN in a tertiary care hospital and compare the efficacy of drug used. **Method:** Data was collected in a preformed proforma and efficacy of the drugs used was assessed by Nerve Conduction Study (NCS) at 0 week and 12th week. Results were analysed statistically. **Result:** Pregabalin was prescribed to 66% patients, Gabapentin to 42% and Amitriptyline to 12%. In NCS, significant improvement was observed by Pregabalin at 12th week in both axonal and demyelinating type of neuropathy, unlike gabapentin and Amitriptyline. **Conclusion:** Pregabalin was the most frequently prescribed and more effective drug than gabapentin and Amitriptyline.

KEYWORDS: Diabetic Peripheral Neuropathy, Nerve conduction study, Efficacy.

INTRODUCTION

Diabetic neuropathy (DN) is the single most common and most distressing late complication of diabetes mellitus affecting nearly 50% of diabetic patients. It is a heterogeneous group of disorder and presents in a wide range of abnormalities affecting different components of the somatic and autonomic nervous systems. Diabetic Peripheral Neuropathy (DPN) comprises more than 50% of all diabetic neuropathies. They can be focal or diffuse, proximal or distal. Of affected individuals, 1 in 4 is symptomatic, almost 50% have objective features identified by clinical examination, and up to 95% have objective signs when evaluated using sophisticated techniques for the assessment of nerve function.[1] Treatment for DPN is not very helpful in many of the cases and therefore it poses a therapeutic challenge to the treating physician and treatment failure and neglected cases are liable to develop foot ulcers and gangrene requiring amputation in certain instances. DPN is responsible for 50% to 75% of non-traumatic amputations.[2] The major morbidity is foot ulceration, which can lead to gangrene and ultimately to limb loss. DPN of the lower limbs also has a tremendous impact on patient's quality of life predominantly by causing weakness, ataxia, and incoordination predisposing to falls and fractures.[3] Management of DPN requires long term use of drugs with doubtful efficacy and safety issues. Antidepressants remain the first-line agent in the treatment of diabetic neuropathy in many centres, but they have considerable safety and tolerability issues which need to be kept in mind while treating neuropathic pain.[4] The anticonvulsants are another class of drugs which have stood the test of time in treatment of diabetic neuropathy. Drugs that can be used include carbamazepine, gabapentin, pregabalin, topiramate, lamotrigine.[5] Selection of medication for the management of diabetic neuropathy is challenging, with individualization of doses, attention to potential adverse effects and drug interactions, quality of life before and after medication so as to ensure patient compliance.[6] Hence this study is aimed to assess the Drug utilization pattern in patients with diabetic peripheral neuropathy (DPN) in our tertiary care teaching hospital and to analyse the efficacy of the drug used in DPN by Nerve conduction study.

METHOD

This is a prospective, observational study conducted in collaboration with Department of Neurology of S.C.B. Medical College and Hospital, Cuttack, a premier tertiary care Hospital in Odisha. The plan of study and the parameters studied were as follows and it was approved by the Institutional Ethics Committee of S.C.B. Medical College & Hospital, Cuttack, before the onset of the study.

Plan of study

Objective	No of Patients	Parameter studied	Visits
Demographic profile of patients	50	Age, Sex, Body wt., Type of diabetes, Duration of diabetes	Initial visit
Drug Utilization study	50	Drug, Dose, Frequency, Duration	Initial 4th Week 12th Week
Efficacy assessment	35	Nerve Conduction Study	Initial 12th Week

Study design & Study population: The study was conducted on patients of Diabetic Neuropathy attending the Neurology O.P.D. of S.C.B. Medical College & Hospital over a period of one year. The Study Protocol, Case Record Form, and Informed Consent Sheet was prepared by the study team and approved by the Institutional Ethics Committee after which patients satisfying the following Inclusion & Exclusion Criteria were enrolled in this study. Informed consent of patients obtained.

Inclusion criteria: The diagnosed cases (by Nerve Conduction Study) of Diabetic Peripheral Neuropathy(DPN) of the lower limb, with symmetrical, mixed sensory-motor Diabetic neuropathy cases, suffering from both axonal and demyelinating neuropathy with adequate glycaemic control and those who are Committed to report for follow-up at 4th and 12th week were included in this study.

Exclusion criteria: The neuropathy cases of non-diabetic origin, those with associated co-morbid conditions (CVA, CHF, IHD, ESRD, Liver disease) were excluded from the study.

Study procedure: The patients attending the Neurology outpatient department (O.P.D.) for complaints of signs and symptoms of Peripheral Neuropathy were screened for Diabetes Mellitus and other diseases known to be causing Peripheral Neuropathy. Once the diagnosis of Diabetic Peripheral Neuropathy was confirmed by the treating clinician, the patients were questioned for their willingness to participate in the study. The patients were explained about the nature of the study and the need of their regular follow up at 4th week and 12th week, and to stay in contact throughout the 12 week period. They were also informed about their right to withdraw from the study at any stage. The consenting patients were enrolled into the study.

Study of patient's Demographic profile: After obtaining the informed consent of the enrolled patients, details of their demographic profile viz. name, age, sex, address, body weight, were recorded in case record form. This was followed by careful history taking

regarding the duration of diabetes, diagnosis of type of DM, present complaints, investigations undertaken, history of present medication(s) including their dose, frequency and duration, which were all noted down in the Case record form designed for the study.

Study of Utilization Pattern of Drugs used for Diabetic Neuropathy: The name of the drug prescribed for the treatment of their diabetic peripheral neuropathy, the class of drug, the dose, dosage form of drug, frequency of administration, duration of therapy, and other adjuvant drugs prescribed were noted down in the Case Record Form. From these data the current drug prescribing trends in the treatment of diabetic neuropathy was assessed.

Efficacy assessment of drugs by Nerve Conduction Study: The study patients were carefully examined for the presence or absence of signs and symptoms of peripheral neuropathy by the treating physician. The efficacy assessment of drugs used in DPN was done by Nerve Conduction Study (NCS), during the initial visit and 12th week of follow up visit. In the Nerve Conduction Study (NCS) recorded the latency (in sec), amplitude (in mV) and conduction velocity (in mV/sec), to motor and sensory stimuli, in tibial and popliteal nerves. However out of the 30 patients who consented for follow-up, 6 dropped out for the 12th week visit and only 24 patients successfully completed the study.

Nerve conduction study is an electro-physiological test useful in evaluating patients with diabetic neuropathy and recommended for clinical research studies. It is shown to be symmetrical in patients with diabetic sensory and sensorimotor polyneuropathy, and hence justify unilateral evaluation. This was performed in the study patient using the instrument functioning in the Neurology Out-patients Department. It was used to record the latency of nerve conduction (in sec), amplitude of conduction (in mV) and conduction velocity (in mV/sec), in motor and sensory divisions of tibial and peroneal nerves. It documents the following aspects of neuropathy: Characteristics of the neuropathy, whether it is Axonal or Demyelinating, regarding localization of the lesion i.e. Mononeuropathy vs. Radiculopathy, Proximal vs. Distal, and the severity of the neuropathy was assessed i.e. only Sensory or Sensorimotor, also Prognosis of morbidity was analysed by Pre-treatment and post-treatment follow up. The following measurements are made in the nerves tested: Latency in Nerve Conduction, denotes conduction in faster conducting motor fibres, it is increased in demyelinating neuropathy. Amplitude of Conduction, correlates with density of nerve fibres, it is decreased in axonal neuropathy but intact in demyelinating neuropathy. Conduction Velocity is decreased in demyelinating neuropathy but intact in axonal neuropathy. [7], [8]

These measurements are made in the following nerves: In the Lower limb, for Motor nerve conduction study, Tibial Nerve and Peroneal Nerve was tested. For sensory nerve conduction study, Sural nerve was examined.

Statistical analysis

Analysis of Demographic profile and Drug Utilization Pattern was done using the Chi-Square test and the efficacy of drugs used in DPN was analysed by Paired t test.

RESULTS

Fifty Diabetic Peripheral Neuropathy patients were recruited into the study for analysis of drug utilization pattern. Out of these, thirty patients consented for follow-up on 4th week and 12th week, and were evaluated for efficacy of drugs used. However 6 patients dropped out of their 12th week visit and 24 patients successfully completed the entire period of study.

Demographic profile of DPN patients: Most of the patients (60%) belonged to the age-group of 41-50 years (range 31 – 72 years) with the mean age being 44.5±2.97 years. There were significantly more number of males (70%) than females (30%), all the patients suffered from Type 2 diabetes for a mean duration of 7±0.34 years.

Drug Utilization Pattern in patients with DPN: As depicted in "Fig. 1", out of the 50 patients suffering from DPN, 32 (64%) patients were prescribed with the drug Pregabalin, 11 (22%) patients were prescribed Gabapentin and only 5 (10%) patients were prescribed Amitriptyline, as primary drugs. Two patients (4%) received a combination of Gabapentin and Amitriptyline. Pregabalin was usually administered in a dose of 75 mg twice daily, Gabapentin mostly in a dose of 300 mg twice daily and Amitriptyline as 10mg thrice daily. All the drugs were prescribed for a mean duration of 2 months (range 1 to 3 months), at the initial visit. They were asked to come for follow up visits at 4th week and 12th week, for evaluation of efficacy and assessment of adverse effects of the drug (if any), after which, if found necessary, the drug could be changed. However, in none of the 35 patients who completed the study, the initial drug was needed to be changed within the 12 weeks study period. The other concomitant medications prescribed were vitamins like vitamin B complex (to 56% of patients) and analgesics like aceclofenac (to 24% of patients), or both (to 10% of patients). All the drugs were prescribed orally as tablets or capsules. Maximum number of patients were prescribed drugs from the antiepileptic class (86%), 10% patients received drug

from antidepressant category and the rest 4% of patients were prescribed with a combination of both.

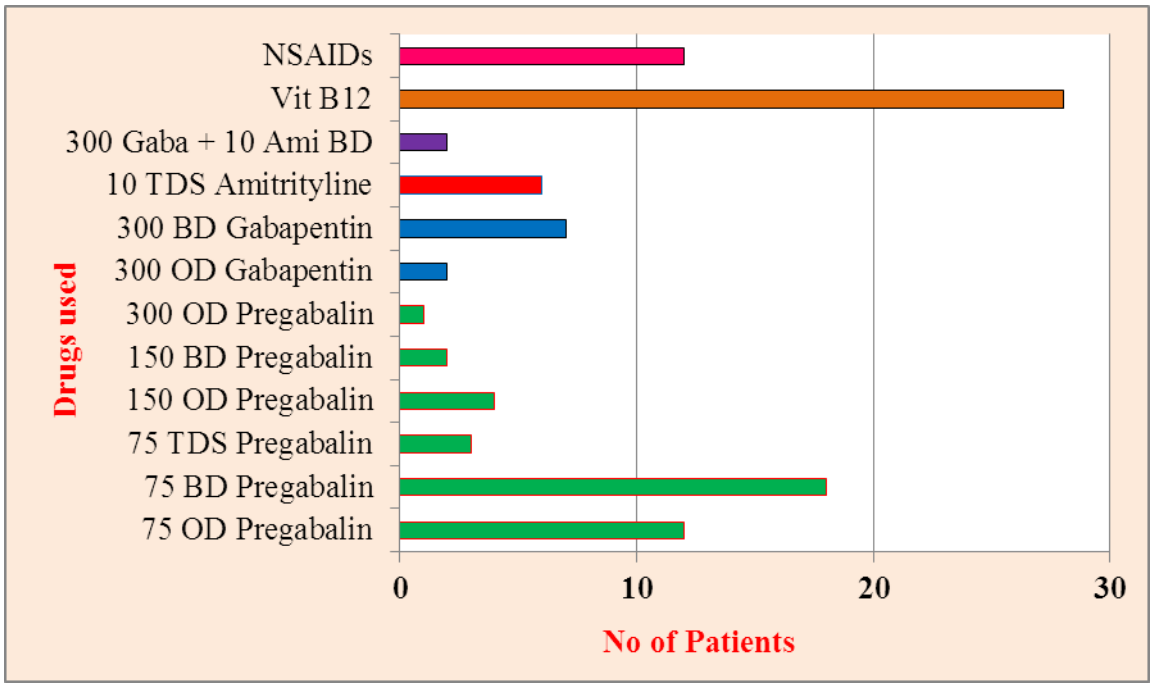

Figure 1. Drug Utillization Pattern of Patients suffering from DPN.

Table 1. Efficacy assessment of drugs used in Axonal Neuropathy by Nerve conduction study.

Nerve studied	NCS parameter observed	Pre-treatment and Post-treatment NCS parameter					
		Pregabalin		Gabapentin		Amitriptyline	
		O wk	12 wk	O wk	12 wk	O wk	12 wk
Peroneal	Amplitude (in mV)	1.15 ± 0.04	1.90 ± 0.04 ***	1.12 ± 0.08	1.13 ± 0.10	1.06 ± 0.09	1.18 ± 0.06
Tibial		2.96 ± 0.06	3.81 ± 0.06 ***	2.68 ± 0.11	2.89 ± 0.08	2.94 ± 0.09	3.02 ± 0.10
Sural	Amplitude (in µV)	3.19 ± 0.06	3.88 ± 0.06 ***	2.97 ± 0.05	2.92 ± 0.09	2.90 ± 0.09	2.94 ± 0.13

*All values are mean ± SEM, Paired t test * = P < 0.05, ** = P<0.01, ***= P< 0.001*

On analysis of Nerve Conduction Study for Axonal Neuropathy (Table 1), comparison of pre-drug (0 week) and post-drug (12th week) values showed significant improvement in amplitude of conduction in Pregabalin treated group only, in both motor and sensory nerves. The improvement in the Gabapentin and Amitriptyline treated groups were not found to be statistically significant in either motor or sensory nerves.

Table 2. Efficacy assessment of drugs used in Demyelinating Neuropathy by Nerve Conduction Study.

Nerve studied	NCS parameter observed	Pre-treatment and Post-treatment NCS parameter					
		Pregabalin		Gabapentin		Amitriptyline	
		O wk	12 wk	O wk	12 wk	O wk	12 wk
Peroneal	Latency (ms)	6.95 ± 0.09	5.85 ± 0.06 ***	6.90 ± 0.27	6.39 ± 0.20	6.68 ± 0.17	6.56 ± 0.19
	CV (m/s)	28.76 ± 0.69	34.29 ± 0.67 ***	27.00 ± 1.38	31.33 ± 1.22	27.20 ± 1.88	28 ± 2.12
Tibial	Latency (ms)	6.90 ± 0.15	5.85 ± 0.11 ***	6.31 ± 0.14	5.84 ± 0.12	6.88 ± 0.15	6.70 ± 0.19
	CV (in m/s)	29.48 ± 0.64	35.33 ± 0.39 ***	29.78 ± 0.68	33.22 ± 1.18	29.80 ± 1.28	30.80 ± 1.16
Sural	Latency (ms)	4.34 ± 0.09	3.52 ± 0.08 ***	4.36 ± 0.27	3.66 ± 0.26	3.74 ± 0.20	3.12 ± 0.25
	CV (m/s)	27.33 ± 0.78	34.38 ± 0.68 ***	29.44 ± 0.91	32.11 ± 0.84	31.00 ± 2.21	32.60 ± 1.96

*All values are mean ± SEM, Paired t test * = P < 0.05, ** = P<0.01, ***= P< 0.001*

On analysis of Nerve Conduction Study for Demyelinating Neuropathy (Table 2), comparison of pre-drug (0 week) and post-drug (12th week) values showed significant improvement in both latency and conduction velocity in the Pregabalin and Gabapentin treated groups, in both motor and sensory nerves. The improvement in the Amitriptyline treated group was not found to be statistically significant in either motor or sensory nerves.

DISCUSSION

The present study is a prospective observational study, being undertaken to assess the effect of Pregabalin, Gabapentin and Amitriptyline used in the management of Diabetic peripheral neuropathy at Neurology O.P.D. of our Hospital. Out of the various types of DPN, Distal Symmetrical Peripheral Neuropathy (DSPN) is the most common type (75%), and hence this subset of DPN patients were included in the study, for uniformity of results

Fifty patients satisfying the inclusion and exclusion criteria were included into this study at initial visit, but 15 dropped out due to unexplained causes and rest 35 completed the study. Hence, analysis of demographic data was done for 50 patients, while the efficacy analysis was done for 35 patients only. On analysis of the demographic profile of the DPN patients it was observed that most of them belonged to the age group of 50 to 60 years (42%), with the mean age being 52.25 ± 12.34 years and age range 29-75 years. This is in concurrence with other studies; in the BIRDEM study,[9] conducted at Dhaka in 2006, the mean age of DN patients was 50.8 ±10.6 years and females were significantly younger than males (48.7 vs.

53.1 years) while in another study[10] at North Central Nigeria in 2003, the mean age was 54.9±12.1 years, with an age range of 22 to 87 years. These reports substantiate the facts in literature that advanced age is a risk factor for DPN.[11] In our study majority of the patients were males (72%) and only 28% were females. Literature review reveals that DPN has a gender predilection with males suffering more than females.[12] All the patients recruited in our study suffered from type 2 diabetes, and none from type 1diabetes. The mean duration of diabetes among the study population was 7.84 ± 6.24 years, most of them suffered from diabetes for a period of 1 to 5 years (46%), while 38% suffered from diabetes for 6 to 10 years. This is similar to the findings in the BIRDEM study,[9] where the mean duration of diabetes was 7.0±1.8 years, and was similar in males and females, and in the Nigerian study,[13] it was 8.4±6.9 years.

On analysis of the Drug Utilization Pattern in patients of DPN in our hospital, it was observed that Pregabalin is the most frequently prescribed drug (66%). This was followed by Gabapentin in 18% patients and Amitriptyline in 12% patients. 4% patients were prescribed with a combination of Gabapentin and Amitriptyline. Though many medications are available for the treatment of diabetic neuropathic pain like tricyclic antidepressants, gabapentin, pregabalin, duloxetine, topical lidocaine, capsaicin, carbamazepine, oxcarbazepine, phenytoin, lamotrigine, and opioids, concern regarding side effects demand proper choice of drug in an individual patient.[4] In the present study, this trend in pharmacotherapy could be due to the recent reports which state that Pregabalin is the most recent anticonvulsant medication approved by FDA for DPN treatment, and may be considered as a first line agent.[14] Though Gabapentin was in use for long time, for the treatment of DPN before the discovery of Pregabalin, the former has been delegated to a second line drug due to its adverse effect profile, especially sedation.[15] Similarly Amitriptyline, a common antidepressant used with success for treating neuropathic pain has now become a third line agent due to its concomitant adverse anticholinergic side-effects. [15] The dose of Pregabalin prescribed in our study varied through a wide range, from 75 to 300 mg/day depending on their symptoms. Even Gabapentin dosing varied from 300 to 600 mg per day as per the symptoms. Amitriptyline was prescribed in a constant dose of 10 mg thrice daily to all the 5 patients. In our study, Gabapentin and Amitriptyline were prescribed in the lower to moderate dose range only, as further increase in dose would cause greater increase in adverse effects; it was justifiably observed that a combination of Gabapentin and Amitriptyline was preferred to higher dose of individual drugs, for treatment of severe resistant pain. The results of the

present study suggests clearly that Pregabalin is the most frequently prescribed drug for diabetic neuropathy in our set up, followed by gabapentin and Amitriptyline.

There are many ways to assess neuropathy. The nerve conduction study is more powerful test and can help in diagnosing subclinical and clinical cases and together with few scoring systems can help in prompt evaluation of the diabetic sensorimotor polyneuropathy. The amplitudes, velocities, latencies, outcome and grading of neuropathy in nerve conduction studies when compared with neurological detection scores showed a significant relation with each other.[16] In our study pregabalin seemed to be more effective in improving nerve conduction. While gabapentin and Amitriptyline failed to elicit improvement in the latency, amplitude and conduction velocities in the demyelinating type of neuropathy, and in the sensory division of the nerve, at 12th week of observation, pregabalin was able to do so. In a study by Chen et al observed that Pregabalin dose dependently inhibited ectopic activity from injured afferent nerve in rat model. In another study by Yuricho et al 2005, four weeks after the start of treatment, there was a significant improvement in minimal F-wave latencies of the median (P<0.001) and tibial (P<0.001) nerves, and in distal latencies (P=0.01) and sensory nerve conduction velocities (P<0.001) of the median nerves. Amplitudes of motor and sensory responses did not change significantly. These findings were similar for patients with type 1 (n=8) and those with type 2 (n=39) diabetes. Further research in this line by randomized controlled clinical trial, in a large number of patients is necessary to confirm the above findings.

CONCLUSION

Pregabalin is the most frequently prescribed drug in diabetic peripheral neuropathy in our set-up, followed by Gabapentin and Amitriptyline. Pregabalin was also more effective in producing symptomatic relief at 4th week of observation than gabapentin or amitriptyline. Pregabalin alone was effective in improving nerve conduction in both axonal and demyelinating type of mixed sensorimotor neuropathy, at 12th week of observation, whereas the other two drugs were ineffective in improving nerve conduction in the demyelinating variety.

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