Original Article

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Pharmacology Section

Screening and Assessment of Polyneuropathy in Diabetic Patients and the Effect of Vitamin B_{12} Administration on the Course of Neuropathy

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ABSTRACT

Introduction: Diabetic polyneuropathy is a specific form of axonal neuropathy that includes peripheral neuropathy of sensory nerve fibers with eventual autonomic and motor involvement. Screening and identification of polyneuropathy offers a crucial opportunity to prevent further complications by using vitamin B_{12}.

Aim: To assess the occurrence of polyneuropathy in patients with type I and type II diabetes mellitus and evaluate the effect of vitamin B_{12} administration on the course of polyneuropathy.

Materials and Methods: This prospective open label study was carried out in 50 patients in medicine Outpatient Department (OPD) at Smt. Kashibai Navale Medical College and General Hospital, tertiary care hospital in Pune, Maharashtra, India. Fifty patients, aged 18-60 years of type I and type II diabetes mellitus were screened for polyneuropathy from June 2016 to June 2017. Thirty two out of 50 patients showed evidence of neuropathy based on either of the parameters including Diabetic Neuropathy Symptom (DNS) questionnaire; Survey of Autonomic Symptoms (SAS) questionnaire; standardized nerve conduction studies and peripheral neuropathy testing {ankle reflex and Diabetic Neuropathy Examination (DNE)}. These 32 patients were given a tablet methylcobalamin 1.5 mg daily for three months after which all the above parameters were repeated to evaluate the course of neuropathy by paired t-test.

Results: Mean baseline DNS score was 1.63±0.75 which improved significantly (p=0.032) to 1.41±0.80 after three month methylcobalamin treatment. Mean baseline SAS score was 4.94±2.60 while post methylcobalamin therapy it was 4.59±2.39, suggesting significant improvement (p=0.009). Nerve conduction velocity of ulnar nerve in every patient was normal before and after methylcobalamin therapy. Mean baseline DNE score (3.34±1.73) improved significantly (p=0.027) to 3.06±1.54 after completing three months of methylcobalamin therapy.

Conclusion: Strong positive association was found between diabetes-Vitamin B_{12} deficiency and polyneuropathy. Administration of methylcobalamin therapy is warranted as it significantly improves symptoms of polyneuropathy in diabetic patients.

Keywords: Diabetic neuropathy, Methylcobalamine, Survey of Autonomic Symptoms

INTRODUCTION

Diabetic Polyneuropathy (DPN) is a specific form of axonal neuro-pathy associated with diabetes that includes peripheral neuropathy of sensory nerve fibers with eventual autonomic and motor involvement [1]. Diabetic Autonomic Neuropathy (DAN) is one of the least understood and recognised complication of diabetes, despite it significantly affects quality of life and survival of diabetic people [1,2].

One of the subtypes of diabetic polyneuropathy is the peripheral neuropathy of sensory nerve fibers which precedes the autonomic and the motor involvement. It represents an insidious and progressive process that initiates the pathophysiological pathway to leg ulceration and amputation and by itself it is sufficient cause for painful paresthesia, sensory ataxia [3]. Screening and identification of this type of neuropathic process offers a crucial opportunity for the patient to implement foot care before onset of significant morbidity.

Perkins BA et al., in their study concluded that annual screening for diabetic neuropathy should be conducted using superficial pain sensation testing, vibration testing by on-off or timed method to predict the likelihood of peripheral neuropathy [4].

Jayaprakash P et al., confirmed the usefulness of simple bedside screening tests for evaluation of diabetic peripheral neuropathy which include ankle reflex, vibration sensation and superficial pain sensation testing [5].

One of the earliest manifestations of diabetic autonomic neuropathy is denervation of cardiovascular system which is also labelled as Cardiac Autonomic Neuropathy (CAN). The prevalence of CAN varies between 1-90% in patients with Type 1 Diabetes Mellitus (T1DM) and 20%-73% in patients with T2DM. This huge variation in CAN prevalence is due to the inconsistency in the criteria used to diagnose CAN and significant differences in the study populations, particularly in relation to CAN risk factors (such as age, gender and DM duration amongst others) [6-8].

DAN may manifests as constipation, gastroparesis, resting tachycardia, exercise intolerance, orthostatic hypotension, impaired neurovascular function, hypoglycemic autonomic failure, erectile dysfunction and sudomotor dysfunction [8]. There is a need to consider all these manifestations while assessing a patient for presence of autonomic dysfunction.

Zilliox L et al., designed a questionnaire to provide a succinct evaluation of autonomic symptoms in subjects with mild neuropathy and suggested it as a sensitive, easy to use tool to detect even a mild autonomic neuropathy that could potentially aid in the early diagnosis of diabetic autonomic dysfunction [9].

Vitamin B_{12} deficiency is a potential comorbidity seen in diabetic patients. In addition to this, many diabetics are treated with metformin, a drug which is known to cause vitamin B_{12} deficiency. One potential health problem from B_{12} deficiency is neuropathy, symptoms of which overlap with diabetic neuropathy [10,11].

Sun Y et al., gave a systematic review of clinical controlled trials on effectiveness of vitamin B_{12} on diabetic neuropathy stating that vitamin B_{12} therapy has beneficial effects on sensory symptoms of neuropathy such as pain and parasthesia although effect on vibration perception is inconsistent. The study also stated that methylcobalamin also improves autonomic symptoms of the patient [12]. However, more trials are needed to confirm beneficial effect of vitamin B_{12} on diabetic neuropathy.

Many authors have mentioned about the possibilities of presence of polyneuropathy at the onset of diabetes or even before the DM is clinically evident [13]. Therefore, it would be of great help in resolving the question of whether a subject can present with the symptoms or signs of polyneuropathy even before major changes in glucose tolerance have developed and whether vitamin B_{12} therapy in such patients can revert the symptoms of early neuropathy so as to prevent further complications.

MATERIALS AND METHODS

Approval for the study was obtained from the Institutional Ethics Committee prior to the conduction of the study. In addition, written informed consent was obtained from each study participants.

Study Design

It was a prospective open labeled study carried out in 50 patients in medicine OPD at Smt. Kashibai Navale Medical College and General Hospital, tertiary care hospital of Pune, Maharashtra, India from June 2016 to June 2017. Patients of both genders aging between 18 and 60 years were included in the study. All patients having prediabetes, type 1 and type 2 diabetes mellitus were included in the study.

Pregnant women, alcoholic individuals and known cases of Guillain Barré Syndrome (GBS), myasthenia gravis, rheumatoid arthritis were excluded. Patients on antidepressants, antipsychotics, over the counter antihistamines, cough/cold preparations, diuretics or any drug that interferes with autonomic testing were also excluded from the study.

Neuropathy Parameters:

Subjects were included considering inclusion and exclusion criteria and demographic characteristics like age, gender;, duration of diabetes, history of autonomic dysfunction, recurrent foot ulcers, concomitant illness and smoking; and mean Fasting Blood Sugar (FBS) and Post Prandial Blood Sugar (PPBS) level were recorded in case record form. Following parameters were used for the screening and assessment of polyneuropathy.

DNS Score: All the selected subjects were given DNS questionnaire form. Form includes four questions related to peripheral neuropathy [14]. The questions were answered either as YES (positive:1 point) or NO (Negative:0 point). Maximum score was 4 and minimum score was 0. Score of ≥1 was considered significant.

SAS Questionnaire: All the selected subjects were given SAS questionnaire form [9]. SAS scale assesses both presence and severity of autonomic symptoms. 11 and 12 questions were there for females and males respectively. Number of symptoms was reported 0-11 for females and 0-12 for males. Total symptom impact score was calculated by summating the rated severity of individual SAS scores.

Standardised Nerve Conduction Studies: Nerve conduction velocity of ulnar nerve was measured by technicians who remained blinded to the status of the patient. Conduction velocity values were taken as parameter stating as normal or abnormal [15].

Peripheral Neuropathy Testing: It was carried out by a second examiner who was blinded to the history, group of the patient and results of the questionnaire assessment.

Ankle Reflex: It was noted whether ankle reflex was present or absent.

DNE scoring: It includes muscle strength, reflex and sensation related to right leg and foot. Maximum score is 16 points. Score of >3 were considered significant for presence of neuropathy [16].

STATISTICAL ANALYSIS

All the data was recorded in the case record form and Microsoft Office Excel and presented as mean±SD for numerical data. All the study parameters were analysed using paired t-test with p-value of <0.05 considered as statistically significant.

RESULTS

Demographic Characteristics

Out of 50 diabetic patient included in the study 17 were male while 33 were female. Mean age of the patients was 52.96±6.77 years that were having diabetes for 5.84±3.86 years. Six patients and four patients gave history of having autonomic dysfunction and recurrent foot ulcers respectively. Majority of the patients (32 out of 50) gave concomitant history of hypertension. History of hypothyroidism and psoriasis were present in one patient each. Three patients were having history of smoking. Mean fasting and post prandial blood sugar levels were 119.9±56.61 mg/dL and 191±85.78 mg/dL respectively [Table/Fig-1].

Neuropathy Parameters

Thirty two out of 50 patients showed evidence of neuropathy based on either of the parameters including DNS questionnaire, SAS questionnaire; standardised nerve conduction studies and peripheral neuropathy testing (ankle reflex and DNE). These 32 patients were given a tablet methylcobalamin 1.5 mg daily for three months after which all the above parameters were repeated to evaluate the course of neuropathy.

DNS Questionnaire

Mean baseline DNS score was 1.63±0.75 which was improved significantly (p=0.032) to 1.41±0.80 after three month methylcobalamine treatment [Table/Fig-2].

SAS Questionnaire

As shown in [Table/Fig-2], mean baseline SAS score was 4.94±2.60 while post methylcobalamine therapy it was 4.59±2.39. These data suggest significant improvement (p=0.009).

Variables	n
Age (Mean±SD) (years)	52.96±6.77
Gender	
Male	17
Female	33
Duration of diabetes (Mean±SD) (years)	5.84±3.86
History of autonomic dysfunction	6
History of recurrent foot ulcers	4
History of concomitant illness	
Hypertension	32
Hypothyroidism	1
Psoriasis	1
History of smoking	3
Mean fasting blood sugar level (Mean±SD) (mg/dL)	119.9±56.61
Mean post prandial blood sugar level (Mean±SD) (mg/dL)	191 ± 85.78

[Table/Fig-1]: Demographic pattern of study population

Neuropathy parameter	Score (Mean±SD)		p-value (paired t-test)
	Before methylcobalamine treatment	After methylcobalamine treatment	
DNS* score	1.63±0.75	1.41±0.80	0.032
SAS† score	4.94±2.60	4.59±2.39	0.009
DNE‡ score	3.34±1.73	3.06±1.54	0.027

[Table/Fig-2]: Neuropathy parameters before and after methylcobalamine treatment.
* Diabetic Neuropathy Symptom, † Survey of autonomic symptoms,
‡ Diabetic Neuropathy Examination

Standardised Nerve Conduction Studies

Nerve conduction velocity of ulnar nerve in every patient was normal before and after methylcobalamine therapy.

Peripheral Neuropathy Testing:

Ankle Reflex: Ankle reflex was present in all the patients at baseline and follow up examination.

DNE Scoring: As depicted in [Table/Fig-2], mean baseline DNE score (3.34±1.73) improved significantly (p=0.027) to 3.06±1.54 after completing three months of methylcobalamine therapy.

DISCUSSION

Diabetic polyneuropathy is very common neuropathy especially industrialized countries and it is associated with a wide range of clinical manifestations. It is mostly seen after 50 years of age and in patients with long-standing diabetes mellitus [17]. Mean age of the patients in the present study was also 52.96±6.77 years and they were having diabetes for 5.84±3.86 years. All the parameters used in the study for screening and assessment of the polyneuropathy are commonly used reliable parameters [9,14-16]. These parameters were suggesting evidence of polyneuropathy in 32 patients out of 50 included patients in the study with few patients having history of autonomic dysfunction and recurrent foot ulcers.

In the present study, there was significant improvement in DNS, SAS and DNE scores after three months oral methylcobalamine therapy. Studies have shown that high doses of methylcobalamin were associated with improved nerve conduction in streptozotocin-diabetic rats [18]. This was further demonstrated in experimental acrylamide neuropathy, where high doses of methylcobalamin significantly increased the rate of motor nerve fibre regeneration [19]. Clinical and biochemical vitamin B_{12} deficiency is highly prevalent among DM patients [20]. Worsening of diabetic neuropathy has also been noted among patients with coexisting vitamin B_{12} deficiency [21].

A systematic review showed that methylcobalamin therapy had beneficial effects on somatosensory symptoms like pain and paresthesia. Three studies included in this review also suggested methylcobalamin therapy benefits on autonomic symptoms, in addition to its effects on pain and somatosensory symptoms [12]. A meta-analysis showed that metformin could decrease vitamin B_{12} levels in a dose-dependent manner and may cause detrimental effects in patients with DM. These kind of patients may also benefit from vitamin B_{12} supplements [22]. A review suggested annual screening for vitamin B_{12} deficiency using more sensitive methods like serum homocysteine and methyl malonic acid concentrations. It has also depicted vitamin B_{12} supplementation should be adopted among diabetic patients with specific risk factors of vitamin B_{12} deficiency [20].

However, a review suggested that pure methylcobalamin and combination vitamin B_{12} therapy were unlikely to be potential candidates for the treatment of diabetic peripheral neuropathy symptoms, although vitamin B_{12} therapy is generally safe and has minimal adverse effects [23]. Therefore, more studies, preferably double blind randomised controlled trials, should be carried out to draw ultimate conclusion regarding efficacy of vitamin B_{12} therapy for diabetic polyneuropathy though the present study was in support of methylcobalamine therapy in diabetic patients.

LIMITATION

Present study had few limitations like sample size was small and it was an open labeled study. Larger sample size might be more impactful. Blinding of the study might avoid the possible observer bias. Measurement of vitamin B_{12} level in the subjects was not done which might lead to clearer conclusion.

CONCLUSION

Polyneuropathy is fairly common amongst diabetic patients. Improvement in multiple neuropathy parameters like DNS questionnaire; SAS questionnaire and DNE after giving methylcobalamine treatment (1.5 mg daily for three months) suggests that it improves in symptoms of polyneuropathy significantly irrespective of vitamin B_{12} level. Therefore, it is advisable to prescribe methylcobalamine in the given dose to all the diabetic patients who are suspected to have polyneuropathy though we still require conducting better studies using larger sample size and proper blinding in the studies.

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