Research Paper

A Novel Potential Role of Vitamin K2-7 in Relieving Peripheral Neuropathy

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Abstract

Objective: To assess the efficacy, tolerability and safety of vitamin K2-7 in patients with peripheral neuropathy (PN). **Materials and Methods:** This study was conducted in 100 patients with PN suffering from VBD or T2DM. Vitamin K2-7 capsules (200 mcg) were given orally for 8 weeks followed up to the 12th week. Symptoms included tingling and numbness along with weakness, fatigue, and cramps. The intensity of the symptoms of PN was assessed on a Visual Analog Scale (VAS). **Results:** At baseline, the VAS score was 6–9 for VBD group and 8–10 for T2DM group. After treatment with Vitamin K2-7 by the 12th week, VAS score had reduced to 1–2 in both groups. The decrease was statistically significant ($P < 0.0001$). **Conclusion:** For the first time, in larger sample size, it has been shown that Vitamin K2-7, 200 mcg for 8 weeks, has a therapeutic activity for the symptoms of PN in VBD and T2DM. The reduction in symptoms was persistent in spite of de-challenge of Vitamin K2-7. Vitamin K2-7 was also well tolerated by all the patients. Thus, it can be concluded that Vitamin K2-7 has potential therapeutic effects for PN due to VBD or T2DM.

Keywords: Peripheral neuropathy, type 2 diabetes mellitus, Vitamin B12 deficiency, Vitamin K2-7

Introduction

Peripheral Neuropathy (PN) is a common problem faced by a large number of patients with its etiology being multifactorial. The most common among them could be Diabetes Mellitus (DM). Currently, 347 million people worldwide have diabetes.[1] India has the largest number of type 2 diabetic patients among the world diabetics. Increased prevalence globally or in India, DM has become a huge economic and health burden to the nation.[2] India is one of the epicenters of the global DM pandemic. Rapid social and economic development and changes in demography and also with increased susceptibility for Indian population have led to the increase in the prevalence of DM in India over the past four decades.[3]

Vitamin B_{12} Deficiency (VBD) is often missed and is frequently neglected. There is a high incidence in the vegetarian population. The manifestations of neuropathy in these conditions vary from mild to severe with symptoms of sensory and motor defects, and it reduces the quality of life and productivity. The neurologic manifestations of folate deficiency overlap with those of VBD and include cognitive impairment, dementia, depression, and commonly PN.[4]

One added cause of iatrogenic neuropathy in DM is the treatment with metformin that leads to VBD.[5] Persistence of neuropathy symptoms despite routine treatment is a well-identified unmet medical need.

The prevalence of symptoms of neuropathy in diabetic population in India is 26%–31%.[6] In an epidemiological survey conducted in India, based on a figure of about 40 million people with diabetes in India, it is estimated that there would be at least 10.4 million people suffering from symptoms of PN.[7] Long-term therapy with metformin is shown to decrease the Vitamin B12 level and manifested as PN.[8] In spite of treatment with Vitamin B12 supplements, the symptoms of neuropathy

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will still be persistent. The same trend is seen in Vitamin B12-deficient patients, where the neuropathy symptoms are persistent despite Vitamin B12 supplementation. This is an observation of an expert hematologist (AAB) which he termed as residual neuropathy.

Two of the authors (DSM and ABV) of the present study had earlier observed that Vitamin K2-7 relieves idiopathic muscle cramps as well as symptoms of diabetic neuropathy.[9] PCT/IN2008/000465, application further claims the safety of usage of Vitamin K2-7 in the various novel conditions such as neuropathy.[10] It was found by anecdotal observation that Vitamin K2-7 helps in relieving neuropathy.

Taking a lead from this serendipitous discovery, it was decided to conduct an open-labeled study of Vitamin K2-7 (MK-7) in 30 patients of PN suffering from VBD and/or type 2 DM (T2DM) in 2009. The study was conducted at BYL Nair Ch. Hospital, Mumbai, and it was shown that Vitamin K2-7 at a dose of 100 mcg twice a day for 8 weeks was well tolerated and safe with a therapeutic activity for relieving the symptoms of PN.[11]

Based on the results of the above study, a larger cohort study was planned to evaluate and confirm the efficacy, tolerability, and safety of Vitamin K2-7 in patients with PN experienced by patients of VBD and T2DM.

Materials and Methods

Study design

An open-labeled observational study for evaluation of efficacy and tolerability of Vitamin K2-7 (MK-7) in patients of T2DM or VBD with PN after approval of the Independent Ethics Committee, Intersystem BioMedica Ethics Committee (ISBEC/NR-14/KM/VM/2015), Vile Parle, Mumbai, was conducted. The trial was registered with the Clinical Trial Registry of India (CTRI) (CTRI/2016/11/007499). Patients were recruited from the Medicine Department of Kokan Hospital, Jogeshwari, Mumbai, India. Patients satisfying the following inclusion and exclusion criteria were enrolled in the study.

The inclusion criteria of this study were as follows: male or female aged 18–65 years suffering from T2DM or VBD with symptomatic diagnosis of neuropathy (>4 on Visual Analog Scale [VAS] score) and willing to give informed consent. The exclusion criteria of this study were as follows: patients suffering from any other illness other than T2DM or VBD, patient participation in clinical trials evaluating investigational pharmaceuticals or biologics within 3 months or admission to study, patients under medications such as corticosteroids and oral contraceptives, patients with seropositive status, pregnancy, patients on coumarin analogs and quinine hydrochloride, and patients who are under history of alcohol and substance abuse within previous 1 year. The primary outcomes were activity and tolerability of Vitamin K2-7 in patients with symptoms of PN suffering from T2DM or VBD as measured on VAS. The secondary outcomes were clinical and metabolic variables.

Study procedure

Patients suffering from PN symptoms due to T2DM or VBD and those found meeting inclusion criteria were enrolled in the study. A written informed consent (informed consent form approved by the Ethics Committee) was obtained from all the patients. Participant confidentiality was maintained throughout the study. After enrollment, the data regarding age, gender, diagnosis, treatment history, and baseline clinical laboratory investigations were recorded in the case record form (approved by the Ethics Committee).

After a proper history, examination and investigations, patients were selected as per the inclusion criteria mentioned in the protocol. Blood investigations, namely complete blood counts with Erythrocyte Sedimentation Rate (ESR), Vitamin B-12, homocysteine, glycosylated hemoglobin, fasting and postprandial plasma glucose, Prothrombin Time (PT)-international normalized ratio, liver function tests, and renal function tests were done at the baseline, at the 4th week, and at the end of the study. The patients were assessed at follow-ups at the end of the 1st, 2nd, 4th, 6th, 8th, and 12th weeks. A detailed physical (general and systemic) examination was done at the baseline and at every visit. The ambulant patients were given 2 capsules (100 mcg each) a day of Vitamin K2-7 for 8 weeks and followed up to 12th week. The subjective severity of the symptoms of PN was assessed with validated VAS scale from 0 to 10 (nil to unbearable) at baseline and thereafter every week till the end of the 12th week. This scale has been used in various studies to measure the intensity and severity of various symptoms of neuropathy.[12] This score was recorded in a patient diary (approved by the Ethics Committee). The safety was assessed by clinical tolerability, side effects, and adverse events and by any change in the organ function tests. The therapeutic activity was assessed by noting the reduction in the severity of the symptoms of PN, namely tingling and numbness along with weakness, fatigue, and cramps as compared to the baseline. Any other effect during the therapy – beneficial or adverse – was also recorded.

Complete blood counts were done by the PC 210 ERMA blood cell counter. ESR was done by Wintrobe method. Liver function test and renal function test were done by biochemical method. PT was done by coagulation method. Fasting and postprandial plasma glucose was estimated by GOD–POD enzymatic method. Glycosylated hemoglobin was measured by boronate affinity method on NycoCard. Vitamin B-12 and homocysteine were done by RIA/ELISA/CLIA method.

Vitamin K2-7 was supplied by Synergia Life Sciences Pvt. Ltd., in the form of capsules (100 mcg) packed 30 capsules per bottle. The capsules were supplied in bottles to patients at the time of the enrollment and at an interval of every 15 days. A patient ingested a 100 mcg capsule every morning

immediately after breakfast and immediately after dinner for 8 weeks. The drug compliance was judged by counting the capsules in the bottle brought back at the follow-up visits. The patient was said to be compliant if he had consumed minimum 80% of the total dispensed capsules.

Vitamin K2-7 capsules were clinically tolerated well by all the patients. Five mild adverse events were reported, which were said to be unrelated to the test substance as judged by the principal investigator. No serious adverse events were reported during the period of therapy. Biochemical investigations and the organ function tests were in normal limits at the baseline, at the 4th week, at the 8th week, and at the end of the 12th week.

Statistical analysis

The statistical analysis of the VAS score was done by one-way analysis of variance test using the Statistical Package of the Social Science (SPSS) version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

One hundred and seven patients aged 18–60 years were screened. Out of 107 patients, 100 patients completed the study [Figure 1]. The baseline data of the two groups were comparable with respect to demographic data and clinical variables of patients with PN [Table 1].

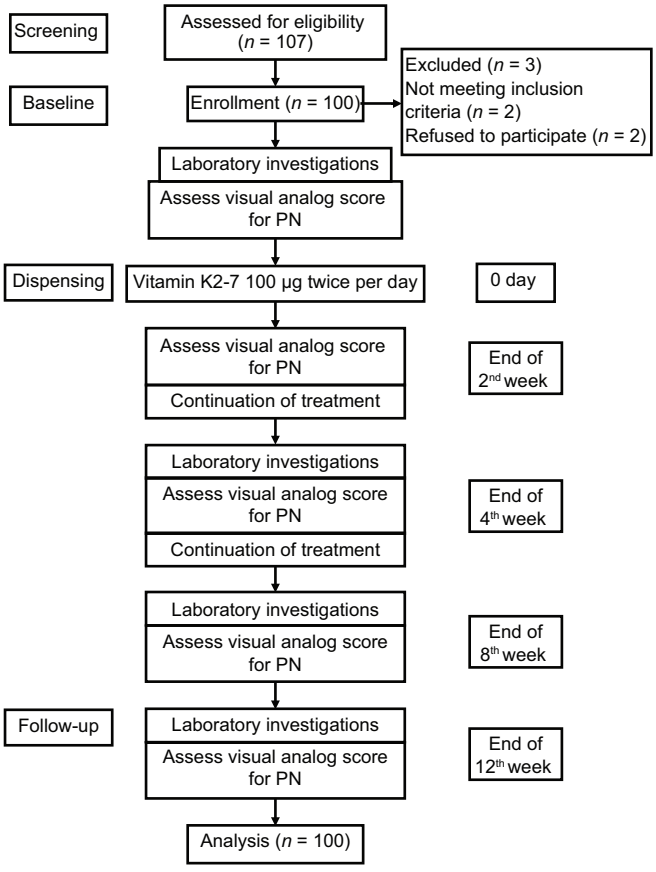

Figure 1: Study flowchart

Patients from VBD group had VAS score of 6–9 at baseline and patients from T2DM group had VAS score of 8–10 at baseline.

By the end of the 4th week, after taking Vitamin K2-7 (200 mcg/day), the VAS score in VBD group had reduced to 4–7 and the VAS score in T2DM group had reduced to 6–8. There was a reduction in the intensity of the symptoms of tingling and numbness. Patients had started experiencing better with the therapy. The associated conditions such as weakness and fatigue had also reduced. Patients, who had also complained of cramps, had reduced number of cramps. The intensity of cramps in VBD patients and burning pain in T2DM patients had reduced to a greater extent.

By the end of 8 weeks after giving Vitamin K2-7 (200 mcg/day), the VAS score in VBD group had reduced to 3–5 and the VAS score in T2DM group had reduced to 2–5. The tingling and numbness had reduced significantly. There was a significant decrease in weakness and fatigue. Cramps and burning pain were now occasional with decreased intensity. By the end of the 12th week, the VAS score of 1–2 in VBD group as well as in T2DM group indicated a continued relief in the symptoms of PN. Decrease in VAS Score of symptomatology in VBD group and T2DM group are graphically represented. There was a decrease in VAS score of individual symptoms of PN from baseline to the 12th week in VBD group and T2DM group [Table 2]. Data of T2DM group were found to be statistically significant. Data of VBD group were found to be statistically significant.

During the period of trial, patients were advised to refrain from any other medications which will have a potential impact on PN.

Discussion

PN is a global health concern without adequate therapeutic approach. It causes difficulties in daily activities, decreases performance, and increases health-care costs.[13] The most common cause is vitamin deficiencies such as Vitamin B12 and disease conditions such as DM. Other causes are autoimmune disorders, alcohol, heavy metal toxicity, and anticancer

Table 1: Baseline demographic data and clinical variables of patients with peripheral neuropathy

	Vitamin B_{12} deficiency	Type 2 diabetes mellitus
Number of patients (*n*)	47	53
Age (years)	45.36 (8.94)	45.19 (9.04)
Gender		
Men	21	30
Women	26	23
Vitamin B_{12} (pg/ml)	198.30 (48.17)	397.92 (119.44)
Blood sugar (mg/dl)		
Fasting	90.98 (9.36)	156.92 (47.13)
Postprandial	114.31 (7.20)	222.88 (15.03)

Values are expressed in mean (SD). SD=Standard deviation

Table 2: Decrease in visual analog scale score of individual symptoms of peripheral neuropathy from baseline to the 12th week in Vitamin B12 deficiency group and type 2 diabetes mellitus group

	Vitamin B_{12} deficiency ($n=47$)		Type 2 diabetes mellitus ($n=53$)	
	Baseline	12th week	Baseline	12th week
Tingling	8.21 (0.657)	1.68 (0.663)*	8.40 (0.716)	1.91 (0.904)*
Pricking sensation	8.04 (1.370)	1.64 (0.705)*	8.40 (0.716)	1.91 (0.904)*
Burning pain	0.98 (2.680)	0.20 (0.571)*	7.62 (2.350)	1.75 (0.918)*
Cramps	9.06 (12.200)	1.51 (0.777)*	1.81 (3.300)	0.55 (1.290)*

Values are expressed as mean(SD). SD=Standard deviation. *$P<0.0001$-statistically significant

medicines. India, with huge vegetarian population and load of Diabetes epidemic has a huge number of patients affected by PN.

The most common symptoms of PN are tingling, numbness, weakness, tiredness, heaviness, pain, itching, crawling, cramps, muscle twitching tremor, gait abnormality, and sensation of pins and needles.

VBD, a leading cause of neuropathy, of mild-to-moderate nature is often missed and is relatively neglected. It has a high incidence in vegetarian population because of lack of Vitamin B12 intake.[14] The diagnosis of neuropathy due to VBD remains a real challenge for the clinician.

In case of DM, another leading cause of neuropathy, vascular complications are well recognized and account for mortality and morbidity. As a result, there is a rapidly increasing interest in searching new therapeutics or even better searching prophylactic methods. Based on a large number of chemical and pharmacological research work, numerous bioactive compounds have been found, especially in functional food ingredients for diabetes.[15] Musculoskeletal manifestations of diabetes are common and, though not life threatening, are an important cause of morbidity, pain, and disability. The burden from painful diabetic PN appears to be higher with increasing severity of pain. More severe pain leads to a higher impairment in daily functioning, sleep, and health-related quality of life.[16] Health-related quality of life is increasingly viewed as a therapeutic outcome and is gradually gaining the same level of importance as clinical or physiological outcome parameters in T2DM patients.[17]

India has the second largest number of people with T2DM in the world (~69 million individuals as of 2015).[18] Diabetic neuropathy continues to represent a therapeutic challenge as the pain relief is still unsatisfactory.[19] The pharmacological treatments are symptomatic, not focused on the pathophysiological mechanisms, limited by side effects and by the development of tolerance.[20] Persistence of neuropathy symptoms despite treatment makes it an unmet medical need.

A higher prevalence of PN is observed in known T2DM patients 33.7% (95% confidence interval: 31.42–36.01).[21] In a cross-sectional study by Roy *et al*.,[8] the authors have shown that metformin users even for 2 years showed evidence of neuropathy on nerve conduction velocity though their body mass index and postprandial blood sugar were maintained.

It is interesting to know that Vitamin K2-7 also plays a role in the prevention and control of T2DM.[22] Vitamin K2-7 plays a role in carboxylating osteocalcin, a Vitamin K-dependent protein, which has been shown to regulate the glucose homeostasis.[23]

A decade-long study of 38,094 Dutch population aged 20–70 found that the participants who consumed the most dietary Vitamin K were 20% less likely to develop type 2 diabetes than the participants with the lowest intake of Vitamin K.[22] Vitamin K2 is linked to lowered risk of developing type 2 diabetes. The risk of developing type 2 diabetes drops for every 10 mcg increase in Vitamin K2 intake. In this study, participants with the highest intake of K2 consumed 250–360 mcg/day. Thus, higher intake of Vitamin K2 is linked to lower diabetes risk.

It is also known that Vitamin K2-7 reduces the progression of insulin resistance and improves insulin sensitivity.[24] In an attempt to better understand how Vitamin K2 improves insulin sensitivity, researchers from Seoul National University, South Korea, studied 42 healthy male volunteers. Participants were either given 30,000 mcg of Vitamin K2 or a placebo each day for 4 weeks. Vitamin K2 supplementation significantly increased insulin sensitivity and seemed to be related to increased carboxylation (activation) of osteocalcin. Researchers concluded that Vitamin K2 can help regulate glucose metabolism by activating osteocalcin, an endocrine hormone that increases insulin sensitivity in humans.[25]

One of the common complications of diabetes is cardiovascular diseases. It is the leading cause of diabetes-related deaths. Heart disease is two to four times more common in population with diabetes.[26] Vitamin K2-7 plays role in carboxylating matrix Gla protein, a known inhibitor of arterial calcification. It helps in keeping calcium out of the arteries and also supports cardiovascular health.[27] This has been covered by Rotterdam Study[28] and Gast Study.[29] Hence, it is now clear that Vitamin K2-7 has a multifactorial role in the human physiology. The research has moved forward from "Glu-Gla" physiology to disease mechanistic approaches such as redox cycle (unpublished data by Synergia Life Sciences), which can effectively address the underlying mechanism of Vitamin K2-7 and its therapeutic effects in various unrelated areas such as cramps and neuropathy.

To further evaluate the potential role of Vitamin K2-7 in other related disease conditions such as cramps, an open-labeled observation trial was carried out by Mehta *et al*.[9] It was

observed that Vitamin K2-7 effectively ameliorated the symptoms of idiopathic muscle cramps. Toxicity studies conducted by Ravishankar *et al.* have shown that Vitamin K2-7 is nontoxic up to dose of 20,000 mg.[30]

Conclusion

It can be effectively concluded from the current study that Vitamin K2-7 at a dose of 100 mcg twice a day for 8 weeks was found to be well tolerated and has a potential for relief of symptoms of PN in cases of VBD and T2DM. It also helps in relieving the associated symptoms of PN such as cramps, burning pain, weakness, and fatigue. It can be concluded that even after the discontinuation of Vitamin K2-7, the symptoms of neuropathy continued to remain with reduced intensity and severity. This proves the therapeutic potential of Vitamin K2-7. More research is ongoing to identify the mechanistic approach of Vitamin K2-7. Till then, clinical studies such as the current study conducted show the promise of Vitamin K2-7 in PN, especially residual neuropathy which is an unmet need. Vitamin K2-7 offers a confirming therapeutic effect in the PN as shown by this study. Further, a multicentric placebo-controlled randomized double-blind trial can clearly establish the effect of Vitamin K2-7.

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Conflicts of interest

There are no conflicts of interest.

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