

# The effect of vitamin K2-7 in peripheral neuropathy due to Vitamin B12 deficiency and/or diabetes mellitus: A Preliminary Study

Kulkarni VK\*, Upase DP\*, Dound YA\*\*, Jadhav SS\*\*, Bhave AA\*\*\*,  
Mehta DS\*\*, Vaidya ADB‡

## ABSTRACT

**Objective:** To evaluate the activity and tolerability of Vitamin K2-7 (MK-7) in a series of patients with peripheral neuropathy due to vitamin B12 deficiency and / or diabetes mellitus.

**Material and Methods:** An open labeled clinical study was conducted in 30 patients presenting with peripheral neuropathy and suffering from either megaloblastic anaemia (vitamin B12 deficient) and/ or diabetes mellitus. Vitamin B12 levels in blood were estimated at baseline and during therapy. Vitamin K2-7 capsules (100 mcg / capsule, twice a day) was given orally for 8 weeks. Patients kept a regular record of the intensity of the symptoms during the baseline and throughout the study. Symptoms included tingling and numbness along with weakness, fatigue and cramps. The intensity of the symptoms was assessed on a Visual Analog Scale (VAS). They were followed up to 8 weeks. Blood biochemical and organ function tests were studied at the baseline, at the fourth week and at the end of the eight week. Prior to the study Ethics Committee Approval was obtained from the Ethics Committee of T. N. M. C. & B. Y. L. Nair Ch. Hospital. The trial was registered with Clinical Trial Registry of India (CTRI). (CTRI/2012/08/002930). Informed written consent was obtained from the patients before enrollment.

**Results:** Depending on the basal VAS score the patients were divided in a moderate group and a severe group. The moderate group had VAS score of 6-8 and the severe group had a VAS score of 8-9. By the end of eight week, the VAS score in both the groups was reduced to 1-2. The intensity specifically of tingling and numbness has reduced to a much greater extent. It was of interest to observe that ten out of 23 patients of Vitamin B12 deficiency group had residual neuropathic symptoms in spite of adequate levels of Vitamin B12 following vitamin B12 administration. The residual neuropathic symptom score reduced following Vitamin K2-7 therapy. Vitamin K2-7 was well tolerated clinically and found to be safe as per the organ functions in all the patients. No adverse events were reported during the period of therapy.

**Conclusion:** This preliminary study has 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 the symptoms of peripheral neuropathy. However, the therapeutic efficacy needs to be evaluated further in a larger sample size, with a placebo controlled randomised double blind trial.

**KEY WORDS:** Vitamin K2-7, diabetes mellitus, megaloblastic anaemia, peripheral neuropathy, reverse pharmacology.

\* - Department of Haematology, B. Y. L. Nair Ch. Hospital, Dr. A. L. Nair Road, Mumbai Central, Mumbai.  
\*\*- Viridis BioPharma Pvt. Ltd., V. N. Purav Marg, Chunabhatti, Mumbai. \*\*\*- Consultant Haematologist; ‡- ICMR Advance Centre of Reverse Pharmacology in Traditional Medicine, Medical Research Center-Kasturba Health Society, Mumbai. **Correspondence to:** Dr V K Kulkarni, 7, Shefalee, Makarand Society, Veer Savarkar Marg, Mahim, Mumbai - 400016 Email: vitamink2beuropathy@gmail.com

## INTRODUCTION

Peripheral neuropathy is a common problem faced by a large number of patients. Its aetiology is multifactorial. Most common causes would be megaloblastic anaemia and diabetes mellitus. India is considered to be the diabetic capital of the world.<sup>1</sup> The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.<sup>2</sup> Megaloblastic anaemia and vitamin B12 deficiency are often missed and is frequently neglected. There is a high incidence in the vegetarian population. The manifestations of neuropathy in these conditions varies from mild to severe with symptoms of sensory and motor defects which reduces the quality of life and productivity.

One added cause of iatrogenic neuropathy in diabetes mellitus is the treatment with Metformin that leads to vitamin B12 deficiency. Persistence of neuropathy symptoms despite routine treatment is a well identified unmet medical need.

Two of the authors (DSM and ABV) of the present study had earlier observed that Vit.k2-7 relieves idiopathic muscle cramps as well as symptoms of diabetic neuropathy.<sup>3</sup>

Taking a lead from this serendipitous discovery it was decided to conduct an open labeled reverse pharmacological study of Vitamin K2-7 (MK-7) in 30 patients with peripheral neuropathy. Appropriate permission from the Ethics Committee (EC) of T. N. M. C. & B. Y. L. Nair Ch. Hospital was obtained prior to the study. This clinical study was registered with Clinical Trial Registry of India (CTRI). (CTRI/2012/08/002930)

## Material and Methods

### Study Design

This study was an open labeled observational study for evaluation of activity and tolerability of vitamin K2-7 (MK-7) in patients of diabetes mellitus and megaloblastic anaemia with peripheral neuropathy. Reverse pharmacological approach was ap-

plied.<sup>4</sup> The study was conducted at B. Y. L. Nair Ch. Hospital.

### Subjects

For the study 38 patients of age 18-60 years were screened. A written informed consent (approved by the ethics committee) was taken from all the patients. Out of 38 patients screened, 8 patients did not report back. The remaining 30 patients were enrolled in the study. Out of these 30 patients 23 patients (male 13 and female 10) were suffering from megaloblastic anaemia and 7 patients (male 3 and female 4) had diabetes mellitus. The patients were divided in two groups based upon the validated visual analog scale score for the degree of severity of symptoms of peripheral neuropathy (tingling and numbness along with weakness, fatigue and cramps). The group A (Severe) had a VAS score of 8 - 9 and group B (Moderate) with a score of 6 - 8.

### The study procedure and assessments

Thirty patients after a proper history, examination and investigations were selected as per the criteria of choice mentioned in the protocol. Blood investigations viz. complete blood counts with ESR, vitamin B-12, homocysteine, glycosylated haemoglobin, glucose tolerance test, fasting and post prandial plasma glucose, PT-INR, liver function tests and renal function tests were done at the base line, at the fourth week and at the end of the study. The patients were assessed at follow ups at 1st week, 2nd week, 3rd week, 4th week, 7th week and 9th week. A detailed physical (general and systemic) examination was done at the baseline and at every visit. A predesigned case record form (approved by the Ethics Committee) which included a page of adverse events was used. The patients were given 2 capsules (100 mcg each) a day of Vitamin K2-7 (Viridis BioPharma Pvt. Ltd.) for 8 weeks. The subjective severity of the symptoms of peripheral neuropathy was assessed with validated VAS from 0 to 10 (nil to unbearable) before, at the end of fourth week and at the end of therapy. The safety was assessed by clinical tol-

**The subjective severity of the symptoms of peripheral neuropathy was assessed with validated VAS from 0 to 10 (nil to unbearable) before, at the end of fourth week and at the end of therapy.**

erability, 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 peripheral neuropathy viz. 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.

### Methods for organ function tests

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. Prothrombin time was done by coagulation method. Fasting and post prandial plasma glucose was estimated by GOD – POD Enzymatic method. Glycosylated haemoglobin was measured by Boronate affinity method on Nycocard. Vitamin B-12 and homocysteine were done by RIA/ ELISA/ CLIA method.

### Interventional drug, dosage and compliance

Vitamin K2-7 was supplied by Viridis BioPharma Pvt. Ltd., in the form of capsules (100 mcg) packed – 30 capsules per bottle. Drug was supplied in

bottles to patients at the time of the enrollment and at an interval of every 15 days. Patient ingested a 100 mcg capsule every morning and evening after breakfast or snacks for 8 weeks. The drug compliance was judged by counting the capsules in the bottle brought back at the follow up visits. Patient was said to be compliant if he had consumed minimum 80% of the total dispensed capsules.

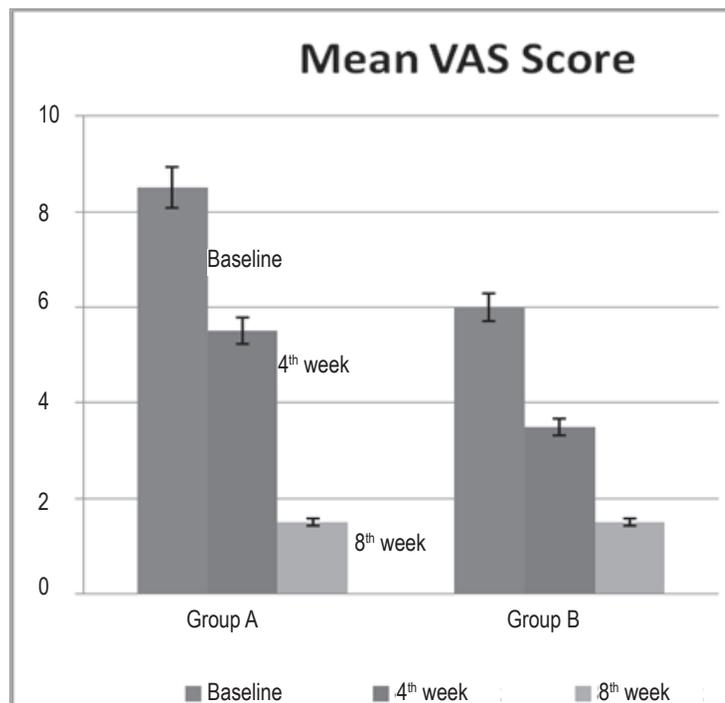
### Results

Patients from the megaloblastic series showed improvement in their blood levels of vitamin B12 on supplementation, However, 10 of them continued to have symptoms of neuropathy despite reaching adequate blood levels of vitamin B12. Majority of the remaining 13 had also shown higher than baseline levels of vit.B12.. Patients from Group A (n=25) had VAS score of 8-9 at baseline. Patients from Group B (n=5) had VAS score of 6 at baseline.

By fourth week, the score in Group A had reduced to 5-6. There was a reduction in the intensity of the symptoms of tingling and numbness. Patients were feeling better with the therapy. The weakness and fatigue had also reduced. Patients who had also complained of cramps were feeling better. The intensity of cramps had reduced to a greater extent. By the same time the score in Group B had reduced to 3-4. The pattern in reduction of the symptoms was similar to group A.

At the end of 8 weeks, in the patients of Group A as well as Group B the VAS score had reduced to 1-2. The tingling and numbness had reduced significantly. There was a significant decrease in the weakness and fatigue. Cramps were occasional with decreased intensity.

It is of a great interest to review a case of 32 year male patient working as a teacher in a school who came with the complaints of tingling & numbness along with pain in both the legs, aggravated by standing for more than 20 minutes and by walking for more than 15 minutes. He was experiencing fati-



gability since 3-4 months. He was enrolled in the study. He was given Vitamin K2-7, 2 capsules (100 mcg each) twice a day. Within 2 weeks the tingling numbness along with pain in the legs decreased. The fatigability improved. Now he was able to stand for a longer time during the lecture. His fatigability also improved a lot. Till the end of the study, i. e. till 8th week, there was no experience of tingling & numbness along with pain in legs and fatigability.

**The current observational pilot study was designed to identify such patients with residual neuropathy and study the effect of vitamin K2-7 in relieving the symptoms of peripheral neuropathy.**

### Tolerability and Safety

Vitamin K2-7 capsule were clinically tolerated well by all the patients. Two 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. The levels of Mean corpuscular volume (MCV) showed a trend which is decreasing. Biochemical investigations and the organ function tests were in normal limits at the baseline, at fourth week and at the end of 8 weeks.

### Compliance

Monitoring of the drug intake during 8 weeks of trial indicated that the drug intake was regular by the patients. This was done by counting the number of capsules remaining in the bottle at the end of 15 days from the date of dispensing the bottle.

### Discussion

Peripheral neuropathy, damage to nerves of peripheral nervous system, can be caused by multiple aetiological factors. The commonest among these are vitamin deficiencies like vitamin B12 and folate and diabetes mellitus. Other causes are auto immune disorders, alcohol, heavy metal toxicity and anti cancer agents. India with her large vegetarian population and burden of diabetes epidemic has a large number of patients suffering from peripheral neuropathy.

Megaloblastic anaemia of mild to moderate

nature is often missed and is relatively neglected. It has high incidence in vegetarian population because of lack of vitamin B12 intake.<sup>5</sup> As judged from clinical practice, vitamin B12

markers are often not done.

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

For the diagnosis of megaloblastic anaemia, there are assays available which detect the levels of vitamin B12 and MCV in the blood.<sup>6</sup> There are various treatment modalities available for this condition. The route of intake remains oral. However in patients with gastro intestinal disturbances, the route of administration available is parenteral by injectables.

Despite good glycaemic control and correction of vitamin B12 through supplements, yet there remain symptoms of neuropathy. This is an observation of an expert haematologist (AAB) which he termed as residual neuropathy.

The current observational pilot study was designed to identify such patients with residual neuropathy and study the effect of vitamin K2-7 in relieving the symptoms of peripheral neuropathy. Five out of thirty patients with residual neuropathy were identified and the therapeutic impact of vitamin K2-7 was identified by considerable relief in the symptoms by a validated VAS scale.

This preliminary observational effect of vitamin K2-7 in peripheral neuropathy due to diabetes mellitus and / or megaloblastic anaemia has indicated therapeutic potential of vitamin K2-7 in these two conditions. Study with a large sample size of residual neuropathy needs to be done..

In a recent publication by Mehta et al 2010, it is seen that Vitamin K2-7 at a dose of 100 mcg / day is helpful in relieving idiopathic muscle cramps.<sup>7</sup>

## Conclusion

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 peripheral neuropathy in cases of megaloblastic anaemia and diabetes mellitus.

## Acknowledgement

*We appreciate the guidance and technical expertise of Dr. Anselm deSouza,, Technical Director, Viridis BioPharma Pvt. Ltd. We thank Dr. S. C. Talwalkar for the laboratory evaluation of biochemical and organ function tests.*

## Conflict of interest:

Dr. Dilip Mehta is CEO and chairman of Viridis BioPharma Pvt Ltd.  
 Dr. Yogesh Doud, Medical Director, Viridis BioPharma Pvt. Ltd.  
 Dr. Shashank Jadhav, Medical Associate, Viridis BioPharma Pvt. Ltd.

## References

1. Joshi SR, Parikh RM. India - Diabetes Capital of the World: Now Heading Towards Hypertension. **JAPI** 2007; 55: 323-24.
2. Wild S, Sicree R, Gojka R et al. Global Prevalence of Diabetes. **Diabetes Care** 2004; 27: 1047-1053.
3. Vaidya Ashok B, et al. Treatment of Human Disease Conditions and Disorders using Vitamin K analogues and Derivatives. PCT/IN2008/000465, Jul. 2008.
4. Vaidya, A. Reverse pharmacological correlates of ayurvedic drug actions. **Indian J. Pharmacol.** 2006; 38:311-5.
5. Oosterhuis WP, Niessen RW, Bossuyt PM et al. Diagnostic value of the mean corpuscular volume in the detection of vitamin B12 deficiency. **Scand J Clin Lab Invest.** 2000; 60:9-18
6. Antony C Asok. Vegetarianism and vitamin B-12 (cobalamin) deficiency **Am J Clin Nutr** 2003;78:3-6.
7. Mehta DS, Vaidya RA, Dound YA et al. Therapeutic Activity and Safety of Vitamin K2-7 in Muscle Cramps: An Interventional Case- Series. **The Indian Practitioner** 2010; May: 287-291.

