



# Therapeutic Activity and Safety of Vitamin K 2-7 in Muscle Cramps: An Interventional Case- Series

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## ABSTRACT

### Objective

To study, the safety, tolerability and therapeutic activity of Vitamin K 2-7(MK7) in a series of patients with idiopathic muscle cramps- systemma

### Material and Method

An open-labelled ambulant trial was conducted in 19 patients presenting with muscle cramps. Vitamin K 2-7 (100µg/Capsule/ Day) was given orally for 3 months. Patients on regular anti-coagulant treatment were excluded from the study. Patients kept the record of frequency, duration and intensity of their cramps during the baseline period of 7 days and throughout the study. They were divided in two groups A and B as per the frequency of cramps. The intensity of cramps was assessed with a Visual Analogue Scale (VAS). They were followed up in the fourth month for recurrence of any cramps. Blood biochemistry and organ function tests were studied at the baseline and at the end of therapy for safety. Prior to the study EC permission and informed consent from patients were obtained.

### Results

Patients from Group A (n=9) had 1-2 cramps/day to 5 /day with severity of 2-9 on the VAS and duration of 1min to 10 min. Patients from Group B (n=10) had lesser frequency of 2-4/wk to at least once a week. Duration of cramps varied from less than 1 min to 10 min with a severity of 2-8 on the VAS. Patients from both the groups experienced a reduction in the frequency. In the Group A, it reduced from 1-2 cramps/day and 5 /day to no cramps or 2-3/month and in the Group B, from 2-4/wk the frequency reduced to no cramps - 1/month. There was also a reduction in the duration as well as severity recorded as 0-3 on VAS as compared to the baseline 2-9 in the Group A. Intensity of cramps was also reduced in the group B from 2-8 VAS decreasing to 0-2 score. Vitamin K 2-7 was well tolerated clinically and found to be safe on the organ function in all the patients. No severe adverse events were reported during the period of therapy.

### Conclusion

Vitamin K 2-7 at a dose of 100 µg /day for 3 months was found to be well tolerated and safe with a therapeutic relief of muscle cramps. The therapeutic activity needs to be evaluated in a larger sample size, with a placebo - randomized cross-over double blind trial to ascertain the efficacy. (*The Ind. Pract.* 2010; 63(5):287-291)

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## KEY WORDS

Vitamin K 2-7, Muscle Cramps, Reverse Pharmacology, Serendipity

## INTRODUCTION

Systemic or muscle cramps are sudden involuntary and painful contractions of the skeletal muscles. Muscle cramps are more common in the old age.<sup>1,2</sup> These commonly occur during sleep and exposure to cold. Cramps occurring without obvious diseases or due to drugs known to cause muscle cramps are termed as idiopathic cramps. Prevalence of these simple cramps in older individual above the age of 60 has varied from 26% in men and 52% in women.<sup>3</sup> Quinine sulphate was the most widely used drug in the treatment of muscle cramps.<sup>4,5</sup> However, quinine has many side effects and some of these can be severe. This makes its use questionable for a benign but highly painful condition of idiopathic muscle cramps. Other drugs used are nifedipine, gabapentine<sup>6</sup> etc. These drugs also have side effects and are even known to cause muscle cramps. There is thus an unmet medical need for filling up this therapeutic gap.

One of the authors (DSM), took vitamin K 2-7 in a dose of 100 microgram/day as a food supplement. He observed that his painful muscle cramps had ceased. The cramps did recur on discontinuation of the vitamin K 2-7 and again subsided on restarting it. This serendipitous finding on the cramp was confirmed by the other author (ABV) in a challenge, dechallenge and rechallenge cycles on himself. Hence it was decided to carry out an experiential interventional study in a case series as per reverse pharmacology path to detect the activity and safety.

In the present article we report the outcome of this observational study of Vitamin K 2-7 (MK-7) in 19 patients with muscle cramps. Appropriate permission from Ethics Committee (EC) was obtained prior to the study and signed written informed consents were taken.

## MATERIAL AND METHOD

### Study Design

This case-series study was observational

and open-labelled for evaluation of clinical safety, organ function and tolerability and therapeutic activity of Vitamin K 2-7 in patients with muscle cramps. The study was conducted at the ICMR Advance Centre of Reverse Pharmacology in Traditional Medicine of the Medical Research Center, Kasturba Health Society (MRC-KHS), Mumbai.

### Subjects

Prior to the study, the permission from the Intersystem Biomedical Ethics Committee (ISBEC) was obtained. Twenty one patients of age 18-81 yrs were screened. A written informed consent (approved by ISBEC) was taken from all the patients prior to their enrollment. They served as their own baseline control. Patients who had muscle cramps associated with endocrine and metabolic disorders were also screened for the study. After a detailed history and a physical examination, patients were instructed to keep a daily record of muscle cramps for seven days prior to their inclusion in the study. Patients who were on regular anti-coagulants treatment were excluded from the study. Out of 21 patients screened, one did not have any cramp during pre-enrollment period and thus was not included and one was not willing to initiate the treatment. The remaining 19 patients (female 13 and male 6) were divided into 2 groups Group A (n=9) and Group B (N=10) depending upon the frequency of cramps viz, cramps every day in group A and 2-3 cramps every week in group B

### The study procedure and assessments

Twenty one patients after a proper history, examination and investigations were enrolled as per the selection criteria for idiopathic cramps. Nineteen of the enrolled patients were given 100µg/day of Vitamin K2-7 (Viridis BioPharma Pvt. Ltd), in the form of capsule for 3 months. The severity of cramps was assessed with Visual Analogue Scale-VAS from 0 to 10 (nil to unbearable) before and after the therapy. Patients were also followed up in the 4th month for any recurrence of the muscle cramps. Blood investigations viz. complete blood counts with ESR, liver function tests,

serum creatinine, fasting and post prandial plasma glucose, serum TSH and LDH were done at base line and at the end of the intervention. Bleeding time and clotting time were also investigated. The patients were serially followed up on 7th day, 30th day, 60th day, 90th day, and 120th day. A detailed physical (general and systemic) examination was done at the baseline and at every follow up visits. A predesigned Case Record Form which included a page of adverse events was used. Safety was assessed by clinical tolerability, adverse events and by organ function tests, therapeutic activity was assessed by noting the difference in the frequency, severity and duration of the cramps as compared to the baseline. Any other effect during the therapy - beneficial or adverse - or carry over activity of the vitamin K2-7 after the discontinuation were also recorded.

#### Methods for organ function tests

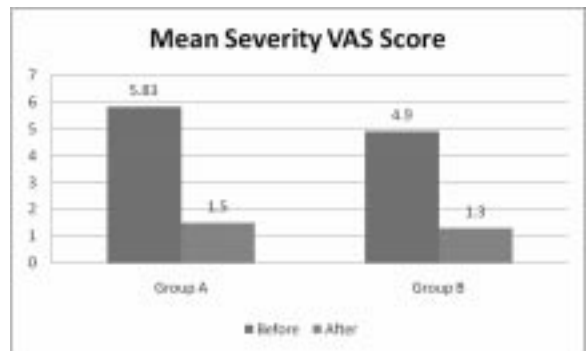
Complete blood counts were done by the cell counter (ERMA-PCE210), liver function tests (SGOT/PT) were done by autoanalyser and the Merck kit. Serum creatinine was assayed by autoanalyser and Spinreact kit. Fasting and post prandial plasma glucose was estimated by GOD-POD method. Serum TSH and LDH was done by ERBA kit.

#### Interventional drug, dosage and compliance

Vitamin K 2-7 was supplied by Viridis BioPharma Pvt. Ltd, in the form of capsules (100 µg) packed - 60 capsules per bottle. Drug was dispensed in bottles to patients at the time of the enrollment and at the end of 2nd month. Patient ingested a 100 µg capsule every morning, after breakfast for three months. The drug compliance was judged by counting the medicine in the bottles at the follow-up visits. Patient was said to be compliant if he had consumed minimum 80% of the total dispensed medications.

#### RESULTS

Patients from the Group A (n=9) had 1-2 cramps/day to 5 /day with severity of 2-9 of VAS and duration of 1 min to 10 min. Patients from the Group B (n=10) had lesser frequency of 2-4/wk to at least once a week.



Duration of cramps varied from less than 1 min to 10 min with severity of 2-8 of VAS. Patients from both the groups experienced a reduction in the frequency except one from the Group B. In the Group A, muscle cramps reduced from 1-2 cramps/day (n=8) to 5 /day (n=1) at base line to 0 cramps (n=8) to 2-3/month (n=1) during therapy. In patients from the Group B, cramps 2-4/wk at baseline were reduced to 0 - 1/month during the therapy. There was also a reduction in the duration and severity recorded as 0-3 on VAS as compared to the baseline 2-9 in Group A. Intensity of cramps were also reduced in group B from 2-8 on VAS score decreasing to 0-2 score as shown in the Figure 1.

At the end of the 3rd month of the therapy, all the patients of the group B had no cramps, while in the Group A occasional cramps (1-2/ month) were still noticed in 5/9 patients. There was a decrease in frequency, severity as well as duration. There was a reappearance of cramps with reduced frequency and severity in both the groups by the 3rd week after the discontinuation of the therapy.

#### Tolerability and Safety

Vitamin K 2-7 capsules were clinically tolerated well by all the patients. Occasionally patients complained of mild constipation. Biochemical investigations and the organ function tests were in normal limits at baseline and at the end of the therapy of three months.

#### Compliance

Monitoring of the drug intake during 3

months of trial indicated that drug intake was only forgotten on when the patient had travelled out of the station for a few days. Recurrence of milder cramps was also noticed when the drug was missed on 3-4 consecutive days.

The study has shown a good therapeutic activity of vitamin K 2-7 for idiopathic muscle cramps as a response was observed in most of the patients. This open labelled experiential study indicates that Vitamin K 2-7 has shown the potential of a safe and active candidate for further studies in relief of patients with idiopathic muscle cramps.

## DISCUSSION

Muscle cramps are a common and quite distressing problem in old age. Its prevalence increases in the elderly age, affecting 30% of > 60 year olds and 50% over the age of 80.<sup>1,2</sup> Underlying pathophysiology of muscle cramps still remains less understood. The conditions known to trigger the muscle cramps are sports, pregnancy, sleep, cold, limb positions etc. They are frequently observed in patients with endocrine/ metabolic disorders. Overexertion, dehydration and electrolyte loss during prolonged sun-exposure etc., can precipitate muscle cramps.<sup>7</sup> Certain drugs are also known to cause muscle cramps.<sup>8</sup> However when they tend to occur without any obvious underlying cause, they are known as 'idiopathic muscle cramps'.

Treatment modalities for muscle cramps vary based often on the diversity of causes. Several treatment modalities are currently in clinical practice with varying degree of success in relieving the symptoms.<sup>9</sup> These modalities include quinine sulphate,<sup>4,5</sup> calcium channel blockers<sup>10</sup>, magnesium,<sup>11</sup> gabapentin,<sup>6</sup> botulinum toxin,<sup>12</sup> phenytoin,<sup>13</sup> Vitamin E,<sup>14</sup> carisoprodol and orphenadrine.<sup>15</sup> In a meta analysis of trials on 659 patients with idiopathic cramps treated with quinine, it was found that there was 24 to 31% reduction in muscle cramps within a period of 4 weeks.<sup>16</sup> However quinine has many side effects such as tinnitus, headache, nausea, tremor, hypotension and gastrointestinal upset. Occasionally fatal hypersensitivity reactions and thrombocytopenia can occur. Quinine amblyopia was reported in a patient

who was suffering from benign nocturnal cramps. There are also side effects like, neurological symptoms, haemolysis, acute renal failure, and arrhythmias. Serious side effects of quinine make its use questionable for a benign but painful condition like nocturnal leg cramps.<sup>16-18</sup> Because of its potential severe toxicity US FDA has banned over-the-counter use of quinine based products.

A serendipitous observation of relief of cramps made by two of the authors (DSM and ABV) of the study strongly emphasizes that the safe vitamin K 2-7 can be studied in an open labelled, observational study for its activity.

Complementary and Alternative system of the medicine provides the description of the similar clinical condition and treatment modalities for the muscle cramps. In Ayurveda, a cramp is described as Pindicodweshtan under the Vatavyadhi. Use of Dashamool (Roots of ten medicinal plants) is the choice of medicine in Vatavyadhi.<sup>19</sup> In the case of Homoeopathy system of medicine, treatment for muscle cramps is mentioned along with various other literatures. Kent repertory of homoeopathic materia medica<sup>20</sup> in the chapter on extremity mentions the use of Magnesium phosphoricum, Chamomila, Natrum Muriaticum, etc. for the treatment of muscle cramps.

In the current study we have observed that a daily administration of vitamin K 2-7 in a dose of 100 µg not only relieved the existing occurrence of muscle cramps but also prevented its recurrence for a while from 4 days to 2 weeks after its discontinuation. Schurgers et al,<sup>21</sup> have shown that the half life of vitamin K 2-7 is 72 hrs. So a cumulative presence of vitamin K 2-7 in the body can explain its longer duration of activity.

It is of great interest to review a subsequent case of a female of 59 years. The patient with severe muscle cramps was referred to MRC-KHS by a haematologist. The severity of the cramps was reaching 9-10 VAS score. Cramps occurred during any time of the day or night. Her jaw will go in to titanic cramps precipitated by a yawn. Her hand muscles went of into cramps while she brushed her teeth. She obtained 70% relief from muscle

cramps after she had already received Vitamin K 2-7 in a dose of 50 µg per day for the past 9 months. The therapeutic activity was noted within a fortnight after she had started Vitamin K 2-7. On discontinuation of the vitamin in between, she had experienced a morbid relapse. This additional case reinforces that even smaller dose could be active therapeutically. An appropriate dose-searching, dose-finding and dose-optimizing study for kinetic-dynamics needs to precede a large scale controlled clinical trial.

## CONCLUSION

Vitamin K 2-7 at a dose of 100 µg /day for 3 months was found to be well tolerated and safe with a therapeutic activity of relief of muscle cramps. A proper dose escalation and a fixed-flexible dosage and a closely monitored compliance with kinetic monitoring, is required with vitamin K 2-7 in muscle cramp. Meanwhile as vitamin K 2-7 is safe and the product is available in a low dosage form of 45 µg, astute clinician can evaluate its effects in clinical settings for systemma - benign but very painful conditions.

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