Original Article

Effect of Vitamin D Supplementation in Dry Eye Refractory to Conventional Treatment

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ABSTRACT

Introduction: Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms. The inflammation has been implicated to play a key role in the pathogenesis of dry eye syndrome (DES). Vitamin D can reduce inflammatory mediators and shows anti-oxidative functions. The aim of the study was to evaluate the improvement in signs and symptoms of dry eye refractory to conventional treatment among DES patients with vitamin D deficiency.

Methodology: A total of 20 patients (40 eyes) of DES refractory to conventional treatment (topical Carboxymethylcellulose or Sodium Hyaluronate when used alone) and with serologically confirmed vitamin D deficiency were supplemented with vitamin D buccal spray (2000 IU) once daily for three months and were followed up at two weeks, one month, and three months and their Tear Breakup Time (TBUT), Schirmer's and Ocular Surface Disease Index (OSDI) scores were evaluated and compared with their corresponding baseline values.

Results: TBUT, Schirmer's, and OSDI scores showed improvement at two weeks, one month, and three months after vitamin D supplementation ($p<0.05$) for all as compared to pre-treatment values. Also, significant improvement in serum 25-hydroxycholecalciferol (25-(OH) D) levels was observed following vitamin D supplementation ($p<0.001$).

Conclusion: Vitamin D supplementation by buccal spray is effective and useful in the treatment of DES refractory to conventional treatment and with vitamin D deficiency.

INTRODUCTION

Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1] Dry eye disease (DED) is one of the common disorders of the eye with an estimated prevalence of 5-30% in population aged 50 years and older.[2] Two main therapeutic approaches are used in the clinic for treatment of dry eye: instillation of artificial tears for tear supplementation and stimulation and instillation of anti-inflammatory drugs to reduce ocular surface inflammation. Artificial tears provide palliative relief of eye irritation in patients with aqueous tear deficiency but do not treat the underlying inflammation or reverse conjunctival squamous metaplasia in chronic DES. Oxidative stress-induced inflammation may be involved in the functional decline of tear production.[3,4]

Low vitamin D level can result in severe symptoms directly, by influencing nociception on nerve fibres and/or indirectly, by lack of negative regulation on dendritic cell activation/migration and inflammatory response. Inflammation aggravated by vitamin D deficiency results in an altered epithelial profile, Bowman layer damage, recruitment of dendritic cells, and altered sub basal nerve plexus features in patients with chronic dry eye disease. Such patients do not respond to conventional therapies and get incomplete symptomatic relief with anti-inflammatory agents like cyclosporine as reported by Shetty et al.[5] Studies have demonstrated that decreasing inflammatory cytokines and increasing anti-oxidant cytokines in tears can improve the symptoms and signs of DES.[6,7] Vitamin D can reduce inflammatory mediators and shows anti-oxidative functions.[8-10] Cornea, the main component of the ocular surface, contains vitamin D receptors and significant vitamin D concentrations, which suggests that vitamin D in the cornea may play a role in the anterior

segment of the eye.[11] Patients with dry eye experience chronic inflammation of the lacrimal gland and ocular surface with high concentrations of several inflammatory mediators including cytokines and T-lymphocytes.[12,13] Tumor necrosis factor (TNF-α), interleukin-1 (IL-1), and IL-6 were detected in the conjunctivae of patients with dry eyes.[14,15] Dry eye is a significant public health issue as it can lead to ocular discomfort, visual disturbance, fatigue, and decreased quality of life. The anti-inflammatory effect of activated vitamin D is achieved by blocking the activation of T-helper cells and cytotoxic T cells and reducing the production of inflammatory mediators such as IL-2, IL-6, IL-8, and IL-12.[16-19] The purpose of this study was to evaluate the role of vitamin D supplementation in dry eye patients who were refractory to conventional treatment and having serologically confirmed vitamin D deficiency.

METHODS

This was an interventional study among 20 patients (40 eyes), carried out at a Research Centre in Jaipur with dry eye symptoms and receiving conventional treatment. Serum 25-hydroxycholecalciferol (25 (OH) D) levels were assessed before starting treatment. Four visits were done during the study (day 0 i.e. day of starting medical treatment, at two weeks, at one month, and at three months of treatment). The optimal level of vitamin D is 50-70 ng/ml. Vitamin D deficiency was defined as serum 25(OH)D levels < 20 ng/ml. Based upon the serum 25 (OH)D levels that ranged from 4 to 51 ng/mL, the values were divided into four groups: severe vitamin D deficiency (<10 ng/mL), vitamin D deficiency (10-19 ng/mL), vitamin D insufficiency (20-29 ng/mL), and vitamin D sufficiency (>30 ng/mL).[20-23] In patients with vitamin D deficiency or insufficiency or severe deficiency and having dry eye, vitamin D supplemen-tation was done by vitamin D buccal spray (2000 IU) once daily i.e. total 1,80,000 IU for three months. TBUT (Tear breakup time), Schirmer's and OSDI (Ocular Surface Disease Index) scores were assessed on day 0, day 14, day 30, and day 90. Vitamin D levels were again assessed at three months.

Quantitative variables were summarized as mean, standard deviations and median. Repeated Measures ANOVA test was used for longitudinal analysis and Post hoc Student-Newman-Keuls test was used for pairwise comparisons. Paired t- test was used to compare vitamin D levels pre treatment and after three months of treatment. 'p' value <0.05 was taken as significant. Medcalc 16.4 version software was used for all statistical calculations.

RESULTS

A total of 20 patients (40 eyes) were included in the study. There were 8 males and 12 females in the present study. After serological assessment of vitamin D levels in dry eye patients, two subgroups of patients were found and analyzed in the study: vitamin D deficient (10-19 ng/mL) and vitamin D insufficient (20-29 ng/mL). The effect of vitamin D supplementation on DES parameters-TBUT, Schirmer's, OSDI scores was assessed at two weeks, one month, and three months.

Overall improvements in OSDI score (n=20 cases), Schirmer's test, and TBUT were assessed using repeated measures ANOVA test and were found statistically highly significant (p<0.001) (Table 1).

Table 1: Overall improvement in Ocular Surface Disease Index (OSDI) score, Schirmer's test and Tear Breakup Time (TBUT) after supplementation of vitamin D among study participants

Variables	At Baseline	After two weeks	After one month	After three months	Repeated Measures ANOVA ('f' value, 'p' value)
OSDI score (n=20)	65.00 ± 15.13	56.50 ± 15.82	48.75 ± 16.29	36.8 ± 17.03	99.551, <0.001
Schirmer's score (n=40) (mm)	6.28 ± 2.21	7.38 ± 2.12	8.98 ± 1.99	10.88 ± 1.98	279.04, <0.001
TBUT score (n=40) (Seconds)	4.25 ± 2.40	6.08 ± 2.14	7.90 ± 2.20	8.72 ± 2.68	197.92, <0.001

Further, pairwise statistical analyses were done with post hoc Student-Newman-Keuls test. There were significant improvements in Ocular Surface Disease Index (OSDI) score, Schirmer's test and Tear breakup time (TBUT) at each time point ($p<0.05$ for all pairs).

Significant improvement in OSDI score was observed at one month and three months compared to pre-treatment values ($p<0.05$). However, at two weeks no significant improvement was observed ($p>0.05$) for vitamin D deficient group but significant improvements were observed at all follow up visits ($p<0.05$) for Vitamin D insufficient group. In both sub-groups (Vitamin D deficient and insufficient), significant improvement in Schirmer's test and TBUT were observed at two weeks, one month, and three months compared to pre treatment values ($p<0.05$ using Post hoc Student-Newman-Keuls test).

Vitamin D levels pre-treatment and post-treatment at three months were evaluated using paired t-test. There was significant improvement in vitamin D levels after three months of treatment compared to the pre-treatment values ($p<0.001$). Mean serum vitamin D levels were pre-treatment and post-treatment are shown in figure 1. After three months of vitamin D supple-mentation by buccal spray, all the patients with deficient and insufficient vitamin D levels showed improvement.

DISCUSSION

Dry eye has been reported to be associated with variety of factors. In the present study, we examined the effect of vitamin D supplementation on DES that was refractory to conventional treatment (topical Carboxymethylcellulose or Sodium Hyaluronate when used alone) in a total of 20 patients with vitamin D deficiency. Vitamin D status was evaluated using serum 25(OH)D concentration. The concentration of 25(OH)D in the blood is regarded to be the best indicator of vitamin D status and it reflects the supply of vitamin D from both the diet and from cutaneous synthesis under the influence of solar ultraviolet light.[24]

Table 2: Improvement in Ocular Surface Disease Index (OSDI) score, Schirmer's test and Tear Breakup Time (TBUT) according to serum 25(OH) D levels among study participants

Variables	Subgroups	At baseline	After two weeks	After one month	After three months	Repeated Measures ANOVA ('f' value, 'p' value)
OSDI score	Vitamin D Deficient (n=8)	70.00±8.86	63.75±9.91	56.25±9.91	41.50±15.43	31.003, <0.001
	Vitamin D Insufficient (n=12)	61.67±17.75	51.67±17.49	43.75±18.11	33.25±17.71	71.954, <0.001
Schirmer's Score	Vitamin D Deficient (n=16)	6.31±1.92	7.38±1.86	8.81±1.76	11.0±1.71	136.91, <0.001
	Vitamin D Insufficient (n=24)	6.25±2.42	7.38±2.32	9.08±2.17	10.79±2.17	147.36, <0.001
TBUT Score (Seconds)	Vitamin D Deficient (n=16)	3.50±1.10	5.44±1.21	7.13±1.41	8.00±2.90	67.90, <0.001
	Vitamin D Insufficient (n=24)	4.75±2.89	6.50±2.52	8.42±2.50	9.20±2.48	132.17, <0.001

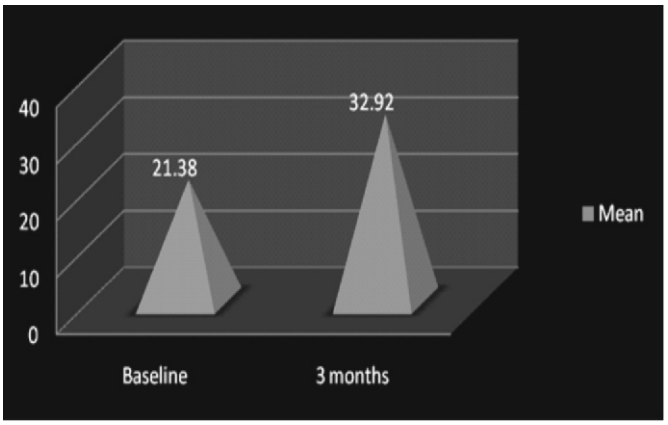

Figure1: Mean Serum 25(OH)D levels pre and post treatment.

Kurtul BE et al[25] reported that TBUT scores and Schirmer's results of the study group were significantly lower than the control group. The mean vitamin D levels were significantly lower in the study group as compared to control. Dry eye symptoms were seen in 100% patients in the study group and 15% patients in the control group. These results were similar to the present study. Shetty R et al[26] studied TBUT scores and Schirmer's and found that the results of the study group were significantly lower than the control group, mean OSDI of patient was significantly higher than in control. There was no correlation between serum vitamin D and TBUT in both patients and controls. In the present study, results showed that the patients with dry eye had lower Schirmer's values, higher OSDI scores and lower TBUT values and inverse correlation between OSDI scores and vitamin D levels.

Dermirci C et al[27] concluded that vitamin D deficiency is associated with tear hyperosmolarity and tear film dysfunction. Our results are in accordance with this study. The patients with dry eye and vitamin-D deficiency had lower TBUT and Schirmer values and higher OSDI scores which improved significantly after vitamin D supplementation, signifying an association between vitamin D deficiency and dry eye.

Yoon SY et al[28] observed that inadequate sunlight exposure time and low serum 25(OH)D level were found to be the main risk factors for DES. These results suggest that sufficient sunlight exposure or vitamin D supplementation may be useful in DES treatment. Similar results were found in the present study. Bae S H et al[29] reported that OSDI decreased significantly at two weeks and ten weeks. TBUT increased significantly at two weeks and six weeks and then returned to pre treatment values at 10 weeks. Schirmer's increased at two and six weeks significantly but at ten weeks there was no significant increase. In the present study, OSDI, Schirmer's and TBUT significantly improved at two weeks, one month, and three months compared to pre treatment values.

As far as supplementation of vitamin D is concerned, the route of administration plays an important role in rising the serum 25(OH)D levels. Satia M C et al[30] compared the absorption of vitamin D_3 through the oral route and buccal spray. It was concluded from the results that the buccal spray produced a significantly higher mean serum 25(OH)D concentration as compared to the soft gelatin capsule, so vitamin D_3 buccal spray for supplementation was used in DES patients with vitamin D deficiency in the present study. In the present study, vitamin D supplementation promoted tear secretion, reduced tear instability, and reduced inflammation at the ocular surface and eyelid margin. Furthermore, vitamin D supplementation improved the symptoms of DES.

CONCLUSION

Vitamin D supplementation by buccal spray is effective and useful in the treatment of patients with DES refractory to conventional treatment and with vitamin D deficiency. Hence, evaluation of serum vitamin D levels in patients with dry-eye symptoms is important and should not be disregarded in their clinical follow up.

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