Role of Vitamin D Supplementation on Symptom Score and Quality of Life in Patients with Chronic Urticaria - A Hospital-Based Randomized Controlled Trial

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KEYWORDS

Vitamin D Supplementation, Add-on Therapy, Chronic Urticaria, Clinical symptoms, Quality of life

ABSTRACT

Background - Urticaria is defined as "a transient, well-demarcated erythematous swelling of the skin, associated with itching, which usually resolves within 24 hours" One-tenth to one-fifth of the total population is likely to suffer from urticaria in a lifetime, while 1% of the general population experience chronic urticaria (>6 weeks). There are few available treatments, where Vitamin D is a possible substitute and safe alternative as an immunoregulatory molecule.

Methods - This is a Randomized Controlled Trial of 100 patients with 50 patients in each group (Group A and B) using UAS7 and CUQ2oL scores. Group A received oral antihistamine (tab. Levocetirizine ranging from 5 mg to 20 mg/day based on the severity of CU, for 12 weeks) along with vitamin D supplementation (60,000 IU of oral vitamin D3 weekly for 4 weeks and one dose at the end of 8 weeks (total 5 doses) and Group B received only oral antihistamine therapy.

Results - After 12 weeks, UAS7 scores in both groups declined considerably, and a larger reduction was found in Group A, and the total CUQ2OL score was also more significantly improved in Group A in comparison to Group B after the study completion.

Conclusion - Add-on therapy with vitamin D3 (60000 IU/week) to subjects with CU can result in a decrease in urticaria symptoms and improve the quality of life of patients over time. So, vitamin D3 could be considered a potentially safe and inexpensive immunomodulator to benefit patients with CU.

ABBREVIATIONS - CU: Chronic urticaria, CIU: Chronic inducible urticaria, CSU: Chronic spontaneous urticaria, 25 (OH) D3: 25-hydroxy vitamin D3, UAS: Urticaria activity score, CUQ2oL: Chronic urticaria quality of life score

INTRODUCTION

Urticaria is defined as **"**a transient, well-demarcated erythematous swelling of the skin, associated with itching, which usually resolves within 24 hours.".[1]

It is considered "acute" when present for less than 6 weeks, and if it carries on beyond 6 weeks, then known as "chronic". .[2]

It was reported that one-tenth to one-fifth of the total population is likely to experience this problem in a lifetime, while 1% of the general population experiences chronic urticaria (CU).

Two types of chronic urticaria (CU) are defined: chronic inducible urticaria (CIU) and chronic spontaneous urticaria (CSU). The latter is also known to be a sudden presentation of wheal and/or swelling without any specific trigger. [2]

The pathogenesis of CU has not been exactly defined. A perivascular infiltration of CD4 lymphocytes and monocytes that is not necrotizing and variable eosinophil, neutrophil, and mast cell accumulation is its defining feature. There are few available treatments, and antihistamines constitute the basis of therapy for symptom management. Systemic corticosteroids, anti-leukotrienes, hydroxychloroquine, dapsone, omalizumab, and other anti-inflammatory medications are probably utilized, but all are likely to carry the risk of severe side effects and high costs. Vitamin D is a possible substitute and safe alternative as an immunoregulatory molecule.[3]

Vitamin D is crucial in boosting immunity because it stimulates both natural and acquired immune responses.[4] According to recent studies, vitamin D is thought to be a negative acute phase reactant that declines with ongoing inflammation.[5] Clinical data support the consideration and usage of vitamin D as a supplement for CU patients, making it a relatively safe and affordable option. Given the foregoing, it is clear that clinical research is necessary to comprehend the clinical advantage of vitamin D. This is especially important because vitamin D insufficiency is thought to affect the Indian population to varying degrees (50–90%).[6]

In the current study, we attempted to compare the reduction in urticaria activity score (UAS) by adding vitamin D supplementation along with standard treatment of antihistamines in comparison to only standard treatment in people suffering from CU as well as to evaluate whether supplementation of vitamin D along with standard treatment decrease medication usage and improve the quality of life in CU patients.

METHODS

This was a hospital-based open randomized control trial that was done on 100 Chronic Urticaria patients attending the OPD of Dermatology, Venereology, and Leprosy, PBH Hospital, Bhubaneshwar. Before the study began, each patient provided a signed informed consent. The patients were randomly allocated to Group A and Group B by concealment (opaque envelope). Group A received oral antihistamine along with vitamin D supplementation, and Group B received only oral antihistamine therapy.

The study included both male and female CU patients suffering from recurring wheals at least three times per week for more than six weeks between the ages of 20 and 60 & who had vitamin D deficiency (serum vitamin D 20 ng/ml). Patients with acute urticaria, physical urticaria, urticarial vasculitis, genetic or acquired angioedema, those who are not vitamin D deficient, decline to give consent, and pregnant or lactating women were excluded from the study.

For all the eligible CU patients, the baseline serum 25(OH) D3 levels were measured, and the qualifying CU cases with serum 25(OH) D3 levels below 20 ng/ml were included in the study. A complete clinical examination and medical history involving the amount and size of wheals, the intensity of itching, the timing and frequency of wheals, and the frequency with which

Antihistamines given in the past were all noted. All patients also underwent a complete blood count, thyroid profile, liver function test, renal function test, and stool examination for ova and cysts.
Urticaria symptom severity and quality of life were assessed for all eligible cases at baseline based on the UAS7 and CU-Q2oL.
The UAS7 is a composite score (scale, 0-6) derived from the daily average morning and evening scores for the severity of the itching (0, none; 1, mild; 2, moderate; and 3, severe) and the number of hives (0, none; 1, 20 hives; 2, 20–50 hives; and 3, > 50 hives/24h) for seven days.
Six aspects of quality of life are measured by the CU-Q2oL questionnaire: pruritus, swelling, and influence on daily activities, sleep issues, limits, and appearance. Patients were asked to rate how upset they were by each facet on a 5-point Likert scale (1 being not at all troubled and 5 being extremely troubled). The total CU-Q2oL score was calculated by adding together the different components, and it was then transformed to a scale from 0 to 100.
Group A (vitamin D supplementation group) was given 60,000 IU of oral vitamin D3 weekly for 4 weeks and one dose at the end of 8 weeks (total 5 doses) along with standard treatment, and those in Group B were given only standard treatment.
H1 non-sedative antihistamine (tab. levocetirizine) dosages ranging from 5 mg to 20 mg per day, depending on the severity of the patient's disease, were the standard treatment used.
As a post-trial responsibility, after completion of the trial, the non-supplemental group also received 60,000 IU of vitamin D once a week for 5 weeks, free of cost.

***Assessment of follow-up*:** After 12 weeks, the cases were followed up on to record UAS, CUQ2oL score, medication use, and side effect monitoring. Comparisons were made between the baseline scores and the 12-week CU-Q2oL and urticaria activity scores.
Additionally, serum vitamin D3 levels were assessed once more for each patient after 12 weeks, and the results were compared to baseline values.

Outcome measure: After 12 weeks, the primary result was evaluated by comparing the decline in UAS7 score after treatment with vitamin D in addition to standard treatment versus only standard treatment.
The impact of vitamin D supplementation on the dosage reduction of medications and the enhancement of patient quality of life with CU were among the secondary outcomes.

Statistical analysis: For statistical analysis, appropriate statistical software, such as MS Excel and SPSS version 24, was utilized. Mean and Standard Deviation were used to present quantitative data. By the findings of the normality test, comparisons between the study groups were made using the unpaired t-test. The Student t-test and Chi-Square test were used to determine whether there was any association between the research groups. The p-value was considered significant if it was less than 0.05.
The study's conclusion involved tabulating and analyzing the data. For each variable, descriptive statistics were generated. Continuous variables were shown to have a regularly distributed mean ± standard deviation.

RESULTS

100 participants were initially enrolled in this study, of which 52 were females and 48 were males. Five patients in group A and four patients in group B were omitted for lack of follow-up. As a result, at the end of the study, 45 patients in Group A and 46 patients in Group B remained till the end of the study.

Comparison of baseline characteristics between Group A and Group B

Parameter	Group A (n=50) Mean±SD	Group B (n=50) Mean±SD
Age (years)	35.54±10.70	37.56±10.40
Gender (M: F)	23:27	25:25
Duration of CSU	1.40±1.13	1.30±0.85
Associated Angioedema	13/50	10/50
H/O Atopy	7/50	10/50
Dermographism	16/50	11/50

Mean serum vitamin D3 levels at baseline were 13.93 in group A and 14.77 in group B. There was no discernible difference between groups A and B's baseline serum vitamin D3 levels at enrollment ($p>0.05$), but became significant at 12 weeks ($p<0.001$). In comparison to group B, group A's serum 25(OH) D3 levels had increased by about 2.8-fold after vitamin D supplementation.

At the end of 12 weeks, a reduction in the mean UAS7 score was observed in both groups compared to baseline, but a significant reduction in UAS7 scores in the vitamin D supplemental group (Group A) in comparison to the non-supplemental group (Group B) was observed. The mean UAS7 score of group A got reduced to 20.76 from 28.60, while in group B, it got reduced to 23.93 from 26.46 in 12 weeks. This means the UAS7 score of group A was not significantly different from group B, as the p-value was greater than 0.05, but it became significant at 12 weeks ($p=0.026$).

The total CU-Q2oL scores were also significantly reduced in both groups ($p< 0.05$) at the end of 12 weeks, with a greater reduction in Group A from a Mean±S.D of 55.20±15.31 to 41.36±19.15 than in Group B from the mean of 59.04±15.83 to 51.98±14.45. Moreover, the mean total CU-Q2oL score was significantly different between both groups at 12 weeks ($p=0.003$) while it was not significant at baseline ($p>0.05$). Among the CU-Q2oL domains, both groups had a considerable decrease in mean scores of practical issues, influence on living activities, swelling, sleep issues, and limitations. But there was no improvement in the mean score for looks observed after the treatment ($p>0.05$).

The antihistamine use was also significantly decreased in both groups at the end of the study, but the difference in the mean antihistamine intake scores between the two groups was not statistically significant.

	Group A Mean±SD	Group B Mean±SD	Across group p-p-value
Serum 25(OH)D3 levels baseline	13.93±3.51	14.77±3.56	0.260(NS)
Serum 25(OH)D3 levels 12weeks	38.52±9.74	14.99±3.61	0.001
Within-group p-value	0.001	0.091	
UAS7 baseline	28.60±7.38	26.46±7.04	0.160(NS)
UAS7 12 weeks	20.76±6.56	23.93±6.84	0.026
Within-group p-value	0.001	0.0167(NS)	
CUQ2OL baseline	55.20±15.31	59.04±15.83	0.24(NS)
CUQ2OL 12 weeks	41.36±19.15	51.98±14.45	0.003
Within-group p-value	0.003	0.0280	
Number of tablets of 5mg levocetirizine at baseline	2.02±0.54	2.02±0.58	0.997(NS)
Number of tablets of 5mg levocetirizine for 12 weeks	1.38±0.53	1.59±0.51	0.06(NS)
Within-group p-value	0.001	0.003	

DISCUSSION

The purpose of this study was to evaluate the effects of vitamin D supplementation on the symptoms and the quality of life of CU patients, as well as the effectiveness of vitamin D as an additional treatment modality when compared to a control group of patients receiving just antihistaminic medication. In our study, CU lasted from three months to a maximum of six years. The mean duration for group A was 1.40 ± 1.13 yrs, and for group B was 1.30± 0.85 yrs. This was comparable to the previous study by Juhlin and Kennard et al.[7,] which showed a similar duration, and in a study by Rather et al[8], the illness lasted between 4 months and 7 years, with a mean of 22.46 months.

***Serum 25(OH) D3 levels*:** Numerous studies have revealed that a link between vitamin D insufficiency and CU risk is quite significant. Patients with CU have 25(OH) D3 levels that are considerably lower than those of healthy subjects.[9] In our study, the vitamin D supplemental therapy significantly raised the serum 25(OH) D3 levels in Group A (2.8 times) while the Group B 25(OH) D3 levels remained largely unaltered. There was no discernible difference between groups A and B's baseline serum vitamin D3 levels at enrollment ($p>0.05$), but at 12 weeks, there was a significant difference in the levels of both groups ($p<0.001$). Similar results were found in research by Mony et al.[10], which showed that after 12 weeks, the 25-OH vitamin D concentrations in the vitamin D group were significantly increased. Rorie et al.[11] also found in their study the similar results.

Urticaria activity score (UAS7): From the pre-treatment to treatment week 12 in both groups, there was a considerable improvement in the UAS7 score, however, group A ($p=0.001$) showed a more substantial improvement than group B ($p=0.016$). Thus, we found that vitamin D supplementation helped in reducing the symptoms and severity in chronic urticaria patients as

Evidenced by a larger reduction in the UAS7 score from baseline to 12 weeks in the vitamin D-D-D-supplemented group in comparison to only the antihistaminic group.
Similar to our study, Araiee et al.[12] found that after receiving vitamin D medication, the severity and symptoms of CIU in study participants statistically decreased. Nabavizadeh et al.[13] found that both low and high vitamin D supplemental groups displayed considerably lower overall urticaria severity scores; at week 6, group 2's score decreased more than group 1's. Boonpiyathad et al.[6], found that following vitamin D treatment, the difference in median UAS7 scores between baseline and after 6 weeks fell considerably (P <0.001) among CSU patients.

Total CU-Q2oL Score: Total CU-Q2oL scores were significantly reduced in both groups ($p< 0.05$) at the end of 12 weeks, with a greater reduction in Group A than in Group B ($p<0.001$). Therefore, the quality of life was more significantly improved in the vitamin D supplementation group in comparison to the other group.
Similar to our study, Topal et al.[9] also found that with vitamin D3 supplementation (300,000 IU/month), CU-Q2oL scores dramatically decreased from 38 to 10.8 from pretreatment to 12 weeks ($p=0.001$). Araiee et al.[12] demonstrated that the treatment with vitamin D supplements affected the enrolled patients' quality of life and greatly improved it. Rasool et al.[13] found that patients who received combined medication (vitamin D plus standard treatment) demonstrated higher resolution of symptoms and quality of life improvements.
In our study, antihistamine usage was also assessed in terms of the number of levocetirizine 5mg tablets patients were taking in the past week at baseline and 12 weeks. There was a significant reduction found in the number of antihistamine tablets intake initially and at 12 weeks in both groups ($p<0.001$ for group A and $p=0.003$ for group B) but there was no statistical difference between the two groups' mean medication scores ($p>0.05$) at the end of the study. Thus, no significant use of vitamin D was found in reducing the medication burden in chronic urticaria patients in our study.

LIMITATIONS

This study was not sufficiently large to be of appropriate precision because it was conducted during a brief period with a small number of patients. Moreover, in Group A, patients were permitted to take antihistamine tablets along with vitamin D. Thus, this study was unable to draw any conclusions about the original effectiveness of vitamin D as a treatment modality.

CONCLUSION

Therefore, add-on therapy with vitamin D3 to subjects with CU can result in a decrease in urticaria symptoms and improve the quality of life of patients over time. So, vitamin D3 could be considered a potentially safe and inexpensive immunomodulator to benefit patients with CU.

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