

Role of Vitamin D in Preventing Relapse and maintaining Remission in Patients with Ulcerative Colitis - A Case Control Study

Khalid Mahmud Khan, Roa Muhammad Tariq, Humaira Alam,
Muhammad Asim Rana, Faisal Naseer, Sumbul Naz

ABSTRACT

Background & Objectives: Ulcerative colitis (UC) affects the mucosa of the rectum and the colon, and is characterized by flares and remission. It is observed that defect of proliferation of T- lymphocytes is the causative factor of ulcerative colitis. Vitamin D appears to play an important role in decreasing the incidence of active UC. The study was undertaken to determine the effect of Vit.D in patients with ulcerative colitis (UC).

Place & Duration of Study: This study was conducted from January 2014 to January 2016 in Mayo Hospital, Lahore, Pakistan.

Methodology: Data was collected from patients suffering from UC who visited the surgical out-patient department and/or were admitted to the surgical floor. A total of 84 patients within the age range of 18-70 years and divided into two equal groups of 42 were included in the study. The control group was given standardized treatment of ulcerative colitis according to severity of disease as measured by Truelove and Witt's criteria. The intervention group was given an additional dose of Vitamin D along with primary disease treatment.

Results: It was seen that patients in the intervention group showed significant remission and a decrease in the frequency of relapses.

Conclusion: Our study supports the hypothesis that vitamin D supplementation helps to achieve significant remission and reduce relapse in patients suffering with active ulcerative colitis.

Keywords: *Ulcerative colitis, Interferon, Vit.D, Remission*

INTRODUCTION

Ulcerative colitis (UC) is associated with an improper deregulated immune response of intestinal mucosa to microorganisms in patients with genetic predisposition. The exact pathogenesis of the disease is unknown but seems to be multi factorial.¹ The evidence based data suggests that inflammatory bowel disease (IBD) advances by activation of T cells and involves the response mediated by helper T cells type 1, 2&17.² Over the past few years, the disease index of UC has increased in third world countries, e.g. in Latin America, Eastern Europe and Asia, except for in a few developed countries.³ In the Asian region, UC is diagnosed at a higher age as compared to western countries. In regards to gender, male predominance is recorded with this disease. In UC, the cumulative risk of mortality is greater in first year after diagnosis, and then declines to a stagnant level around after 22 years.^{4,5}

For the last few decades, vitamin D is believed to have a critical role in the treatment of illness with its major effects on metabolism of phosphate and calcium. The location of Vitamin D on different tissues like monocytes, antigen presenting cells, leukocytes and activated CD4+ and CD8+T cells is now fully understood.⁶

Previous data reveals that 1.25 dihydroxyvitamin D3 inhibits the proliferation of helper T cell type-1 and17, andat the same time stimulates the activity of T regulatory cell. Additionally, Vitamin D seems to

decrease the monocytes differentiation to dendritic cells, thus decreasing the availability of antigen presenting cells for stimulation of T cells.⁷

Vitamin D is mainly produced in skin from 7 dehydrocholesterol under the influence of sunlight. It is first metabolized to 25 hydroxy vitamin D (25OH D)The renal role of vitamin D metabolism involves conversion of 25 hydroxy vitamin D TO 1-25 dihydroxy vitamin D (1,25 (OH)₂D) that controls bone metabolism.^{8,9}

Other pathways involve the uptake of 25-hydroxy vitamin D, either bound and free form (dietary source) with subsequent hydroxylation in cells other than renal system, mainly colonic epithelial cell and monocytes and convert to 1-25 dihydroxy vitamin D which then carry out specific interaction involved in immune mediation.^{10,11}

Vitamin D also has a significant role in immunomodulation. Helper T cells of type 1 produce inflammatory cytokines that include tumor necrotic factor -alpha (TNF- α) and interferony, interleukin-2 (IL-2), all of which play pivotal role in combating infections. Vitamin D3 helps regulate the production of these cytokines.^{12,13} 1, 25 dihydroxy Vitamin D3, enhance the differentiation, maturation and immune-stimulatory capacity of dendritic cells as well.¹⁴ In a retrospective study it was seen that the severity of UC is associated with vitamin D deficiency especially in patients who were on steroids.¹⁵

We conducted this study in Mayo hospital Lahore to determine the efficacy of vitamin D supplementation in maintaining remission and reducing relapse in patients with ulcerative colitis.

Correspondence: *Dr. Muhammad Asim Rana*

Consultant Physician

Department of Critical Care, Medical & Hepatobiliary Services

Bahria International Hospital Lahore

E-mail: drasimrana@yahoo.com

PATIENTS AND METHODS

Study conducted in Mayo hospital Lahore, Pakistan from January 2014 to January 2016. Initial data was collected from 96 adult patients visiting medical out door and admitted on medical floor through same outdoor. All those patients with abdominal X-ray showing sign of toxic mega colon and those with malignant growth on colonoscopy and atypical cells (suspicion of malignancy) on histopathology were excluded. Two patients lost follow up so were removed from study.

From 96 a total of 84 patients, between 18 to 70 years of age were selected. With symptoms suggestive of active disease according to Truelove and Witt's criteria and biopsy proven disease of ulcerative colitis showing inflammatory cells and inflammation of crypts, distortion of crypts, crypt abscess, erosions and alterations for mild, moderate and severe disease and those with vitamin D deficiency (vitamin d levels <30ng/ml) having no history of smoking were included in the study.

Data was collected on specialized questionnaires with basic demographic findings like gender and age. Cases were randomly classified into two groups A and B, each with 42 patients. After randomization, patients of group A and B were both given standard treatment. Group B was given additional vitamin D supplement dose of 50,000 IU intramuscularly, once weekly for 2 months and then fortnightly for the rest of the duration of follow-up.

Rachmilewitz endoscopic score of every subject was calculated at the time of induction and at the end of the study.

**OPERATIONAL DEFINITIONS
CONTROL GROUP**

In this group, the patients with mild disease (Truelove and Witt's score of 6 or less than 6) limited to rectum or recto-sigmoid region were given mesalamine topically as 4g enema, 2 weeks at bedtime plus mesalamine 400 mg 2 tablets TDS orally (2400 mg per day) and ciprofloxacin 500mg BD orally for 6 weeks. For moderate disease (Truelove and Witt's score between 7 and 12) involving the whole colon or recto-sigmoid region, mesalamine topically 4g enema at bedtime plus prednisone oral 0.5 mg/kg (tapering with response), mesalamine 400 mg 2 tablets TDS (2400mg/day) and ciprofloxacin 500mg orally for 12 weeks. The patients having severe ulcerative colitis (Truelove and Witt's score more than 12) limited to any region or involving the whole colon were admitted and started on intravenous regime of hydrocortisone 300 mg QID given for 5 days with mesalamine orally (2400-4800 mg/day) plus mesalamine 4g and hydrocortisone 100mg enema at night and in the morning respectively, and if after 5 days the condition of the patient is improved than prednisone oral 0.5 mg/kg (tapering with response) was started. Ciprofloxacin orally 500mg BD was given for 12 weeks. The patients who achieved remission with mild disease after 6 weeks and moderate to severe disease who achieved remission after 12 weeks were started on maintenance regime of mesalamine orally 400mg TDS.

Rachmilewitz Endoscopic Score for Ulcerative Colitis:

	Study Population n=80	
Granulation (scattering reflected light)	NO	0
	YES	2
Vascular Pattern	Normal	0
	Disturbed/Faded	1
	Absent	2
Vulnerability of mucosa	None	0
	Contact Bleeding	2
	Spontaneous Bleeding	4
Mucosal Damage (mucus, fibrin, erosion, ulcer)	None	0
	Slight	2
	Pronounced	4

Table 1: Histopathology

MILD	MODERATE	SEVERE
Invasion of lamina propria by plasma cells and lymphocytes. Infiltration of surface, crypt epithelium by neutrophils and/ or crypt abscesses present in less than 50% of the crypts	Crypt abscesses and cryptitis involving more than 50% of crypts	Presence of erosion or ulceration

Table 2: Severity of ulcerative colitis assessed by Truelove and Witt's criteria

Features	Mild	Score	Moderate	Score	Severe	Score
Motions per day	<4	1	4-6	2	>6	3
Rectal Bleeding	None/visible blood with stool <half of the time	1	visible blood with stool half of the time or more	2	Passing blood alone	3
Temperature	apyrexial	1	37.1-37.8 degree C	2	>37.8 degree C	3
Pulse Rate	<70	1	70-90	2	>90	3
Hemoglobin	>11 g/dl	1	10.5-11 g/dl	2	<10.5 g/dl	3
ESR	<30	1		2	>30	3

Score 6 or less than 6 = mild disease
 Score 7 - 12 = moderate disease
 Score more than 12 = severe disease

Table 3: Mayo Index Score

Category and Value	Description
Number of Stool	
0	Normal
1	1-2 stools per day more than normal
2	3-4 stools per day more than normal
3	>4 stools per day more than normal
Bleeding P/R	
0	None
1	Blood visible with stool less than half of the time
2	Blood visible with stool half of the time or more
3	Frank blood

Remission: the six points partial Mayo Index score less than 1 and its symptoms subsiding within 2 weeks of treatment are considered as remission.

Relapse: the six points partial Mayo Index of score more than one was considered as relapse and the persistent presence of patient's symptoms even after two weeks treatment were considered as failure for response.

CASE GROUP

In addition to standard treatment, as above, vitamin D supplementation 50,000 IU, intramuscularly, once weekly for 2 months and then fortnightly for rest of duration of follow-up was administered.

COLONOSCOPY

The colonoscopic features suggestive of ulcerative colitis were erythematous mucosa, superficial ulceration, friability, loss of normal vascular pattern and pseudopolyps. It was assessed by endoscopic Rachmilewitz score for ulcerative colitis.

HISTOPATHOLOGY

The histopathological findings considered positive for ulcerative colitis were characterized into mild, moderate or severe disease depending upon the criteria shown in table 1.

MONITORING AND FOLLOW UP

Every patient was monitored daily during the hospital stay and followed every 2 months after discharge, for 6 months and then every 3 months for another 6 months. Remission and relapse was evaluated at every visit according to the relief or aggravation of symptoms and laboratory investigations including CBC, ESR, RFTs, serum Calcium, Vitamin D and Phosphate levels. The Male Index Scoring System was calculated at each visit. Primary outcome were, the number of patients achieving remission and number of relapses in both groups during follow-up.

STATISTICAL ANALYSIS

We designed Quasi experimental study. Statistical analysis was performed by using IBM SPSS version 20. The quantitative variables such as age, laboratory values and Mayo score were presented by using mean. The

Table 5: Remission pattern seen in Treatment and Control group in relation to Age and Gender

Group	Remission		P-value	Relapse		P-value
	Yes	No		Yes	No	
AGE: 18-40yrs			0.00			0.00
Treatment	25	6		7	24	
Control	10	26		26	10	
AGE: 41-60yrs			0.12			0.12
Treatment	6	5		5	6	
Control	1	5		5	1	
GENDER						
Male			0.002			0.002
Treatment	16	6		6	16	
Control	8	19		19	8	
Female			0.003			0.003
Treatment	14	6		6	14	
Control	3	12		12	3	

Table 4: Characteristics of Treatment and Control Group

Characteristic	Treatment group n=42	Control group n=42	P- value
Age			0.17
18-40years	31(73.81%)	36(85.7%)	
41-60years	11(26.19%)	6(14.29%)	
Gender			0.26
male	22(52.38%)	27(64.29%)	
females	20(47.62)	15(35.71%)	
Severity of disease			<0.00)
Moderate left side colitis	16(38.09%)	0(0%)	
Moderate pan colitis	1(2.38%)	10(23.8%)	
Severe Left sided colitis	18(42.86%)	2(4.76%)	
Severe Pan colitis	7(16.67%)	30(71.43%)	
Remission/Relapse			0.00
Remission	30(71.43%)	11(26.11%)	
Relapse	12(28.57%)	31(73.81%)	
Vit D Levels	Mean	Mean	
Pre treatment	16.24	15.81	0.46
Post treatment	54.83	13.69	0.00
Rachmilewitz score for UC	Mean	Mean	
Pre treatment	10.38	10.39	0.13
Post treatment	2.79	5.79	0.00
Trulove and Witts score for UC	Mean	Mean	
Pre treatment	14.95	15.50	0.10
Post treatment	7.52	10.21	0.00
Mayo index Score	Mean	Mean	
Pre treatment	5.67	5.57	0.37
Post treatment	1.83	2.93	0.00

qualitative variables e.g. gender, severity of disease, remission and relapse were represented by frequency tables and percentages. The remission and relapses of ulcerative colitis during follow-up in both groups compared by using chi-square test. P value ≤ 0.05 was taken as significant. P-value was used to see the effect of treatment (pre and post) for remission and relapses of ulcerative colitis.

RESULTS

According to the result of the study 73.81% (n=31) in the treatment group and 85.71% (n=36) in control group were between 18 to 40 years of age, and 26.19% (n=11) in the treatment group and 14.29% (n=6) in control group were between 41 to 60 years of age. P-value found non-significant (Table 4).

As far as gender is concerned, 52.38% (n=22) in treatment and 64.29% (n=27) in control group were male while 47.62% (n=20) in treatment and 35.71% (n=15) in control group were female.

Regarding severity of disease, moderate left sided colitis was recorded as 38.09% (n = 16) in treatment group while no case in control. Moderate pan-colitis was recorded in 2.38% (n = 1) in treatment and 23.81% (n = 10) in control group. Severe left sided colitis was recorded in 42.86% (n = 18) in treatment group and 4.76% (n = 2) in control group. 16.67% (n = 7) in Treatment group were recorded as severe colitis and this severity was found in 17.43% (n = 30) in control group, P-value was significant for disease severity 0.00

As seen in Table 4; Comparison of remission and relapses in both groups after treatment was done and shows the details where the remission was recorded as 71.43% (n = 30) in treatment and 26.19% (n = 11) in control group, while 28.57% (n = 12) in treatment and 73.81% (n = 31) in control group had relapse, P-value was less than 0.05 showing a significant difference between the two groups. Pre-treatment Mayo index score in both groups was calculated as 5.67 in treatment and 5.57 in control group, p-value 0.37 showing insignificant difference. Post-treatment Mayo Index Score in both groups was calculated as 1.83 in treatment and 2.93 and control group, p value of 0.0001 showing a significant difference (Table 4)

With respect to age, maximum remission was seen in 18-40 years among treatment group patients 25/42 as compared to 41-70 yrs age group (6/42), with significant p-value. However relapse is more in control group individuals in same age group 18-40 yrs e.g. 26/42 with significantly p-value (Table 5)

Mean Vitamin D levels in both groups were recorded, it shows that pre-treatment, the levels were 16.24 in treatment group and 15.81 in control group, while post treatment these findings were calculated as 54.83 in

treatment and 13.69 in control group.

Rachmilewitz score for ulcerative colitis was calculated as 10.38 in treatment group and 10.93 in control group, p value 0.13, thus showing insignificant difference. Post-treatment Rachmilewitz score for ulcerative colitis in both groups was computed as 2.79 in treatment group and 5.74 in control group p value was 0.0001 showing a significant difference.

Pre-treatment Truelove and Witt's score for ulcerative colitis in both groups was recorded as 14.95 in treatment group and 15.50 in control group. p-value was calculated as 0.10 showing significant difference. Post-treatment Truelove and Witts score for ulcerative colitis in both groups was calculated as 7.52 in treatment and 10.21 in control group, p-value of 0.0001 showing a significant difference between the two groups.

Pre-treatment Mayo index score in both groups was calculated as 5.67 in treatment and 5.57 in control group, p-value 0.37 showing insignificant difference. Post-treatment Mayo Index Score in both groups was calculated as 1.83 in treatment and 2.93 and control group, p-value of 0.0001 showing a significant difference. (Table 4)

As far as gender is concerned remission is seen more pronounced in males 16/42 similarly with females 14/42 in treatment group p-value found significant. However relapse was high among control group 19/42 and 12/42 in males and females respectively. p-value was also significant in this group.

DISCUSSION

According to our study remission/ relapse in both groups after treatment revealed, remission in n=30(71.43%) in treatment and n=11(26.19%) in control group. While n=12(28.57%) in treatment and n=31(73.81%) in control group had relapse. p-value was <0.05 , showing clear difference between groups. Similar results were obtained in a study conducted by Blanck and colleagues showing remission in 71% of cases with treatment and 29% in control group showing a significant difference between these two groups.¹⁵

Blank S and colleagues in same study examined the relationship between clinical activity and vitamin-D level of patients with ulcerative colitis. They detected 23% of females with mean age around 45.7yrs, these findings corresponds to our study, and however age of patients was slightly higher in our patients. In their selected cases the patients deficient of vitamin D were statistically significant to have more active disease than those with normal levels p-value =0.04. It also signifies the association of status of vitamin D and need for treatment with steroids, and a higher percentage of patients with deficient level (47%) requiring such

management as compared with 7% in control group ($p=0.02$). They concluded that deficiency of vitamin D is common in cases with active ulcerative colitis, especially requiring corticosteroids. Similar to our study, Imogen Nicholson in their systemic review concluded that decrease in diseases activity noted with vitamin D supplementation.¹⁶

CONCLUSION

So, from this study, we can formulate some future model for patients suffering from UC. Vitamin D levels should be checked in all patients with active disease process. Its replacement should be prescribed in routine in order to enhance recovery and remission of primary disease.

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