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ORIGINAL ARTICLE

Protective Effect of Vitamin-D Supplementation in Patients of Acute Coronary Syndrome During COVID-19 Pandemic

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ABSTRACT

Introduction: Objectives: To determine the effect of vitamin-D supplementation in patients of the acute coronary syndrome and its role if any in preventing COVID-19 infection.
Study design: Prospective clinical trial
Place and duration: Armed Forces Institute of Cardiology in collaboration with Riphah International University
Material and methods: The study was conducted by recruiting 40 patients, diagnosed with the acute coronary syndrome. After the PCI procedure during their hospital stay, 20 of them were given a single shot of vitamin-D supplement in a dose of 200000 IU while the rest of 20 were allocated as controls. Patients were instructed to follow the SOPs strictly and were followed up for incidence of coronavirus disease after 2 months. Detailed history regarding their stay during lockdown was taken. Independent sample t-test was used to compare the two groups with p≤0.05 considered as significant.
Results: The patients enrolled in the study were assessed for pre and post-intervention levels for vitamin-D. After the intervention the levels in the experimental group were increased to 30.74±18.40 ng/ml (p=0.000***) from a mean value of 18.27 ±8.98 ng/ml. Among the control group, eight out of 40 patients tested positive for COVID-19 while none among the experimental group got the disease (p=0.016*). The results of the follow-up interview showed that the patients followed the precautions for COVID protection during the pandemic.
Conclusion: Vitamin-D supplementation during lockdown may prove beneficial in protection against COVID-19.
Keywords: Vitamin-D, COVID-19, acute coronary syndrome

INTRODUCTION

Cardiovascular disease particularly acute coronary syndrome is one of the major causes of mortality and morbidity in developed as well as under developed countries[1]. There are many factors contributing towards the disease and its complications. Some are modifiable while others are non-modifiable factors. Among the modifiable risk factors for acute coronary syndrome, one of the emerging risk factor is vitamin-D deficiency[2]. As the process of atherosclerosis involve underlying inflammation of the coronary vessels, and vitamin-D deficiency has been associated with increased risk of inflammation and its deficiency may be associated with increased risk of thrombotic events as well[3]. Vitamin-D plays an immune modulatory role [4] by affecting the cellular immune response and has an immunosuppressive effects on the cytokine release[5].

The novel coronavirus 2019 infection (COVID-19), a worldwide pandemic, has been declared a public health emergency all over the world. The patients who presented with the COVID-19 infection showed a constellation of symptoms with marked variability in clinical severity ranging from mild flu, sore throat and fever to a more severe presentation including pneumonia, severe acute respiratory distress syndrome (SARS-CoV-2), micro vascular thrombosis, myocarditis, and cytokine storm. The underlying mechanism in all these complications includes inflammation. As there are no treatment options currently available to cure COVID-19 infection, the emphasis is focused towards the preventive modalities.

Studies have also linked vitamin-D deficiency as a risk factor for corona virus disease[6,7]. COVID-19 disease predispose the patients to thrombotic events. The acute coronary syndrome patients along with concurrent corona virus infection present with more thrombus burden[8,9]. Low levels of vitamin-D are also associated with an increase in cytokine storm which provides an evidence for the presentation of myocardial injury among the COVID-19 patients. Vitamin-D has been demonstrated to down regulate the production of inflammatory cytokines, such as TNF-alpha and IL6, while increasing inhibitory cytokines[10]. These studies raise the possibility that adequate levels of vitamin-D may reduce the incidence of cytokine storm, which can occur in COVID-19. The use of vitamin-D supplements enhances innate immunity by promoting phagocytosis, suppresses pro-inflammatory cytokines and increases anti-inflammatory cytokines[11].

With the resurgence of COVID-19 pandemic with new variants, it has become imperative to look for the public health measures that can help in preventing the severe form of the disease and can also reduce the case fatality rates. In the current pandemic, there are studies showing the vitamin-D deficient state linking with increased complication rate of COVID-19 infection but the data regarding the role of supplementation in prevention of COVID-19 infection in acute coronary syndrome patients is limited. If the vitamin-D supplementation reduces the severity of COVID-19 in regard to inflammation, cytokine storm and thrombotic events then it would be relatively safer and easier option to reduce the impact of pandemic. This study was aimed to determine the role of vitamin-D supplementation in preventing the incidence of COVID-19 disease.

MATERIAL AND METHODS

The prospective clinical trial was conducted at Riphah University in collaboration with Armed Forces Institute of Cardiology (AFIC) Rawalpindi, Pakistan, after approval from Ethical review committee (App# Riphah /IRC/19/0377) of Riphah University. The total duration of the study was 6 months.

Inclusion criteria:

- Patients diagnosed with ACS of age up to 70 years
- No recent history of intake of vitamin-D supplementation
- PCI done
- No history of kidney disease

Exclusion criteria:

- More than 70 years of age
- Patients taking vitamin-D supplementation
- Unstable patients awaiting for PCI to be done
- History of kidney disease
- History of hyperparathyroidism & hypercalcemia

A total N=40 patients diagnosed with acute coronary syndrome having the PCI (percutaneous coronary intervention) procedure done were included in the study. All the patients were recruited from AFIC. Informed consent was taken. Those who consented for the study were further subdivided into 2 groups. A total of n=20 patients were allocated to control and experimental group each. Pre-sampling was done and the experimental group received 200000 IU of vitamin-D as a single oral dose. Nothing was administered to the control group. Post sampling was done after an interval of 2 months. Vitamin-D levels were assessed using 96-well ELISA kit. The ELISA procedure was performed for all the samples using the serum vitamin-D ELISA kit with Catalog Number: 10501. The optical density (OD) at 450 nm was read with the micro plate reader within 15 minutes of procedure. After post sampling, the patients were interviewed in detail for the incidence of COVID-19 disease. Details regarding exposure to COVID-19 cases (among family and closed contact), stay at homes during lockdown and preventive strategies to prevent COVID-19 disease (use of face mask, social distancing and hand washing) were enquired.

RESULTS

Descriptive statistics of the study patients are given in table-I. There was no significant difference between the two groups in terms of demographic profiles.

Table 1: Demographic profile of patients included in the study

Variable	Control group (n=20)	Experimental group (n=20)	p value
Age (years)	53.70 ± 11.50	54.10 ± 8.03	0.799
Gender (male)	20	20	1.000
Weight (Kg)	79.90 ± 15.57	85.50 ± 14.32	0.345
Diagnosis	NSTEMI= 65% U.A=35%	NSTEMI=55% U.A=45%	0.809
Smoker	Smoker = 40% Non-smoker =60%	Smoker = 60% Non-smoker =40%	0.224
Diabetes	Diabetic =35% Non-diabetic = 65%	Diabetic =35% Non-diabetic = 65%	1.000
Hypertension	Hypertensive =45% Normotensive =55%	Hypertensive = 55% Normotensive = 45%	0.602
Family history	Positive = 70% Negative = 30%	Positive = 65% Negative = 35%	1.000
Vitamin-D (ng/ml)	16.10± 5.9	18.27 ±8.98	0.547

The variations in serum Vitamin-D concentrations in both control and experimental groups are given in table-II.

The serum vitamin-D levels in the control group were decreased significantly from a mean of 16.10±5.90ng/ml to mean of 10.20 ±3.99ng/ml. In the experimental group, the serum vitamin-D levels were increased significantly from 18.27±8.98ng/ml to a mean of 30.74±18.40ng/ml.

Table 2: Comparison of mean vitamin-D levels in control and experimental groups

	Pre-vitamin-D levels (ng/ml ±SD)	Post-vitamin-D levels (ng/ml ±SD)	p value
Control group	16.1±5.90	10.2±3.99	0.000***
Experimental group	18.27±8.98	30.74±18.40	

The effect of intervention among the control and experimental groups was compared by using the independent t-test. The mean level of vitamin-D in control group was 10.20 ±3.99ng/ml while in experimental group the mean value was increased to 30.74 ±18.40ng/ml. This test showed p value of 0.000*** which was highly significant, showing that the vitamin-D increased the serum values of the intervention group.

The post sample interview of all the patients was carried out, in which 4 out of 20 patients among the controls reported to be COVID-19 positive (p=0.016*) (table-III). A detailed history of symptoms were taken. All the patients were symptomatic with fever, body aches and dyspnea. The average time duration of the illness was 2 weeks. The interview of experimental group showed that none of the patients got COVID-19. Exposure history was taken from all the patients. The 6 patients from experimental group admitted positive exposure from family members who suffered from symptomatic infection with fever, body aches and loss of smell but none of patients came positive for COVID-19. Patients remained at homes during lockdown and followed the precautionary measures for COVID-19. The independent t-test was used to determine the effect of intervention in preventing the infection among the patients.

Table 2: Comparison of mean vitamin-D levels in control and experimental groups

Sr. no.	Groups	Total number N=40	COVID-19 positive	p value
1.	Control group	n=20	4	0.016*
2.	Experimental group	n=20	0	

DISCUSSION

The study was aimed to determine the vitamin-D status of acute coronary syndrome patients during lock down and effect of vitamin-D supplementation in improving the status and preventing COVID-19 infection. The current lifestyles followed by urbanized population has increased the risk for vitamin-D deficiency which ultimately can increase the risk of many illnesses which are linked to vitamin-D deficient state including diabetes, hypertension, cardiovascular diseases, inflammatory diseases and respiratory infections[12].

The results of the serum vitamin-D concentrations in the present study in patients of acute coronary syndrome shows deficient state with the mean value of 17.18 ± 7.58ng/ml. The control group showed a mean value of 16.10 ± 5.90ng/ml. While the experimental group showed mean of 18.27±8.98ng/ml. The result of this study has demonstrated that vitamin-D given in a single high dose of 200000 I.U can increase the serum levels significantly (p=0.000***). The mean serum levels in the control group showed a decreasing trend from a mean of 16.1±5.9ng/ml to 10.2±3.99ng/ml. The possible reason behind this might be the fact that the patients remained indoors due to the global pandemic of COVID-19[13]. On the contrary, the experimental group showed that the levels were increased to 30.74±18.4ng/ml from 18.27±8.89ng/ml. The samples were collected after 4 months which was the period of lock down due to the global COVID-19 pandemic. Previous researches have also shown that the administration of a single high dose of vitamin-D can effectively raise the vitamin-D levels[14]. Another study conducted by Malcolm et al. has also proved that single large doses can effectively raise the plasma concentration of vitamin-D at least for 3 months[15]. So, this should be preferred over daily doses which may be ineffective in improving the vitamin-D status due to poor compliance.

The results of the present study have demonstrated that 8 out of 40 patients (20%) among the controls became COVID positive during this pandemic while none of the patients among the experimental group showed positive result. This was despite the fact that they got positive exposure history from the close contacts (family members). The results of this study are unique in its significance that the data regarding the clinical trials investigating the effect of vitamin-D supplementation in preventing corona virus disease is limited. Vitamin-D is involved through multiple mechanisms in preventing the viral infections, these include affecting innate immune response, increasing cellular immunity by lowering the cytokine storm[16]. There is evidence that human DPP/CD26 receptor form a link with a glycoprotein virulence factor, S1 domain of COVID-19 spike[17]. The expression of this receptor is reduced after correction of vitamin-D deficiency. COVID-19

infection induces inflammatory condition in the body increasing CRP and pro inflammatory cytokines which predispose patients to ARDS, pneumonia and thrombotic conditions[18]. Case fatality rate as well as inflammatory response is high in vitamin-D deficient subjects infected with COVID-19[19]. A clinical trial by Kim C. Ohaegbulam et al. showed that patients receiving vitamin-D supplements showed improved clinical recovery and decreased cytokine storm[20].

The severe form of corona virus disease results in complications and multi-organ involvement. The cardiovascular system may get affected resulting in myocardial infarction, myocarditis, heart failure and venous thromboembolic events[9]. The incidence of acute coronary syndrome increases with concurrent viral infection, the mechanism being destabilization of plaque due to inflammatory storm. The patients of corona virus disease-2019 presenting with raised cardiac troponin levels are associated with adverse outcomes[22]. Vitamin-D deficiency is common in patients of acute coronary syndrome which predisposes them to increase susceptibility of COVID-19 disease. Hence, the maintenance of optimal levels of vitamin-D should be considered patients of acute coronary syndrome. It is recommended that vitamin-D status should be assessed in every patient suffering from acute coronary syndrome and vitamin-D deficiency should be corrected in such patients to prevent the possible complications of the deficiency. The limitations of the present study are small sample size due to financial constraints. It is recommended that future studies may be conducted on large population.

CONCLUSION

Vitamin D deficiency is a modifiable factor and a single large dose of vitamin D supplementation improved vitamin D status among the experimental group. There was decreased incidence of COVID-19 demonstrating the protective effect of vitamin D in preventing the infection rate. Vitamin D, a safe and cheaper option, can be used in protection against COVID-19 infection.

Limitation of study: The major limitation of the study was small sample size. Baseline serum parathormone and calcium must have been done. Randomization was also not possible which makes the internal validity of the study of less power.

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