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Original Article

Effectiveness of Vitamin D in Prevention of Dengue Haemorrhagic Fever and Dengue Shock Syndrome

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Abstract

Background: To compare the risk and severity of development of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome(DSS) in patients receiving Vitamin D supplement compared to those not receiving it.

Methods: Diagnosed patients of DF (n=124) were enrolled in this comparative study. Patients were randomized into two groups having 62 participants in each group. Group A received single dose of 200,000 IU Vitamin D and Group B received no intervention. Both groups were followed for development of DHF or DSS. Chi square was applied to compare the groups.

Results: One patient (1.6%) in Group A developed DHF. Seventeen (27%) patients in Group B progressed to DHF. The relationship between Vitamin D and progression to DHF was significant, X2 (2, N=170) =16.43, p= 0.000). The calculated relative risk was 0.0588 (95% confidence interval, .0081 to .4285; p for trend = 0.0588).

Conclusion: Vitamin D decreases the risk of DHF and may have a role in management of dengue fever.

Key Words: Vitamin D, Dengue fever, Dengue haemorrhagic fever

Introduction

Dengue is a febrile illness that is a major cause of morbidity throughout the tropical and subtropical regions. It is a caused by a flavivirus with four distinct serotypes (DV-1, DV-2, DV-3, and DV-4). DHF is characterized by all the symptoms of Dengue fever (DF) along with haemorrhagic manifestations such as spontaneous bleeding, decrease in platelet count and evidence of increased vascular permeability noted as increased haemo-concentration or pleural effusion or ascites. [1] Virus spreads between humans by mosquito vectors of the Aedes genus, i.e, Aedes aegypti and Aedes albopictus.[2] Approximately 2.5 billon people are at risk of getting infection and 50 million cases of dengue fever are reported every year.[3] Infection with any of the serotypes may be asymptomatic in the majority of cases or may result in a wide spectrum of clinical symptoms, known as Dengue fever. The symptoms of dengue fever range from a mild flu-like syndrome to the most severe forms of the disease, DHF, which includes coagulopathy and increased vascular permeability. DHF may progress to hypovolemic shock known as DSS.[4] In Asia the risk of developing severe disease is greater in Dengue fever-infected children (≤15 years) than in adults.[5]

The life-threatening DSS stage occurs at the time of or shortly after drop in blood pressure, which is characterized by a rapid, weak pulse, narrow pulse pressure (≤20 mm Hg) or hypotension with cold, clammy skin in the early stage of shock. This may soon progress to more serious form of shock if patients do not receive prompt and appropriate treatment, in which pulse and blood pressure become undetectable, resulting in death within 12 to 36 h after onset of shock.[6]

Low blood calcium levels have been associated in Dengue. [7] Calcium has proven to be essential for cytotoxic activity of the dengue type 2 viruses (DV)-induced macrophage cytotoxic (CF2).[8] Calcium appears to play a role in the induction of dengue-specific T-helper cells. Dengue antigen has been shown to increase the influx of calcium into T-cells. The proliferation of dengue-specific T-helper cells appears to be dependent on calcium and is inhibited in the absence of calcium and by calcium channel antagonist drugs.[9] There is some evidence that the production of nitrite in response to dengue virus infection is also calcium dependent and can be inhibited by calcium channel blocking drugs. [10]

Prevention and control of dengue and DHF has become the need of time with the expanding geographic distribution of disease and increased disease incidence in the past 20 years.[11] Unfortunately, tools available to prevent dengue infection are very limited. Despite considerable work on vaccine for DF and DHF over the years, an effective safe vaccine is yet to be developed because of various obstacles. Mosquito prevention is also an important step in eradication of dengue fever. [12-14]

Few studies have also discussed role of Vitamin D in reducing the severity of DF,DHF and DSS. A case

series published in 2009 showed 5 patients receiving Vitamin D had overall improvement of clinical condition and reduced symptoms of DF.[15] A Brazilian study found increase in Vitamin D binding protein in DF.[16] The possible explanation of anti- dengue effects of vitamin D is because of involvement of cathelicidin (in the form of LL-37), human beta defensin 2, and through the release of reactive oxygen species.[17] Presently it is believed that patient of DF will never progress to DHF or DSS but wide variation in severity and outcome of disease make this doubtful.

Patients and Methods

A total of 124 patients with diagnosed dengue fever, who fulfilled the inclusion criteria were enrolled in to the study from 01.9.2016 to 31.1.2017 from Benazir Bhutto Hospital after getting ethical review board approval. Patients were randomized to two groups having 62 participants each. Group A received 200,000 IU Vitamin D and Group B received no intervention. Both groups were followed for development of dengue hemorrhagic fever or dengue septic shock. Data was recorded in self-structured questionnaire. Categorical data was presented as frequencies. Pearson's Chi square was applied to compare the proportion of patients in each study group who will develop DHF & DSS. Relative Risk was measured along with 95% confidence intervals to compare the risk of development of DHF & DSS in both study groups. Significant value was < 0.05.

Results

Total of 124 patients were enrolled after informed consent. Mean age was 33.43 ± 16.20

Table 1: Dengue Fever- variables at presentation

Variables	Mean	Std. Deviation
Age (Years)	33.43	16.22
Calcium at admission (mg/dl)	8.81	.42
Albumin at admission (g/l)	4.44	3.65
Platelet at admission ($X10^9$ /l)	108.90	40.24
HCT at admission(%)	41.9	4.62
WBC at admission($X10^9$ /l)	3.73	1.27
Platelet at discharge($X10^9$ /l)	117.15	49.38
HCT at discharge (%)	40.19	5.12
WBC at discharge($X10^9$ /l)	4.56	1.51

. Mean calcium level at admission was 8.81 ± 0.42. Mean platelet at admission was 108.90 ± 40.24. Mean platelet at discharge was 117.15 ± 49.38 **(**Table 1).Most of the patients were admitted on 3rd ,4th and 5th day(n=105)91.6% (Table 2).

One patient (1.6%) in Group A receiving in Vitamin D supplements developed dengue hemorrhage fever. Seventeen (27%) patients in Group B not receiving Vitamin D supplements progressed to dengue hemorrhagic fever. None of the patients developed DSS (Table 3). The relationship between Vitamin D supplements and Progression to DHF was significant, X^2 (2, N=170) =16.43, p= 0.000. Vitamin D decreases the risk and severity of DHF. The calculated relative risk was 0.0588 (95% confidence interval, .0081 to .4285; p for trend = 0.0588)

Table 1: Total No of Days of Illness

No of Days of Illness	Frequency	Percent
1st Day	2	1.6
2nd day	7	5.6
3rd day	37	29.8
4th day	32	25.8
5th day	36	29.0
6th day	10	8.1
Total	124	100.0

Table 3: Vitamin D Supplementation

Vitamin D	Dengue Fever	Dengue Haemorrhagic Fever
	No(%)	N0(%)
Yes	61(98.4)	1(1.6)
No	45(73.0)	17(27.0)

Discussion

In present study, in group receiving Vitamin D, there was fewer progression of DF to DHF. The relationship between Vitamin D supplements and Progression to DHF was significant, X2 (2, N=170) =16.43, p= 0.000. Vitamin D decreases the risk and severity of DHF. The calculated relative risk was 0.0588 (95% confidence interval, .0081 to .4285; p for trend = 0.0588). A Mexican study investigated the effect of treatment with vitamin D3 on two types of human cell lines (hepatic Huh-7 and monocytic U937) infected with DENV.[18] Pureta found that exposure to 1,25-dihydroxy vitamin D3 significantly reduced the number of infected cells, particularly in monocytic cells, and lowered the production of pro-inflammatory cytokines.[18]Vitamin D3 significantly reduced the levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-12p70 and IL-1β) produced by infected U937 cells. These results suggest that vitamin D3 may represent a potentially useful antiviral compound. According to another study, vitamin D supplementation altered IL-12 expression and dendritic cell maturation.[19] Giving vitamin D to dengue patients improved clinical condition.[19] Standard treatment for dengue management is give electrolytic solutions administration, bed rest, measurements of body temperature, blood pressure, haematocrit, platelet count, and administration of antipyretics.[19]

Host nutritional status is a strong predictor of immunity.[20] Host nutritional status or micronutrient supplementation as adjuvant therapy could lower the probability of progressing from DENV infection to overt/severe forms of disease or reduce disease severity in patients.[22] Low blood calcium levels have been associated with Dengue.[7] The mean calcium level at admission at our study was 8.81±0.42.

In present study only 1 patient on Vitamin D developed DHF. Alagarasu et al showed that there might be an association related to the inducing effect of vitamin D on Fcγ-receptor expression. Fcy receptor enhances viral entry into cells, possibly leading to higher viral load in dengue cases with secondary infection and the development of DHF or dendritic cell-specific intercellular adhesion. Studies Vitamin D might influence viral entry into cell. [21]

Albuquerque compared protein levels in the plasma of patients with severe DF with the protein levels of healthy individuals and found that a one of the proteins showing a significant increase in DF patients was vitamin D-binding protein.[18] Sánchez-Valdéz observed a significant increase in platelet count on receiving vitamin D in their clinical trial. The average platelet count changed from 136,000 ± 69,508 cells/mm3 before treatment to 179,600 ± 56,584 cells/mm3 after treatment.[15] In our study the mean platelet at admission was 108.90±40.24, while at discharge it was 117.15±49.38.

The mean haematocrit at admission was 41.9±4.62 while at discharge it was 40.19±5.12. Sánchez-Valdéz also observed a significant improvement in the overall clinical condition of the patients as well as reduction in the duration of signs and symptoms of the infection. Sánchez-Valdéz suggested that Vitamin D supplementation may possibly restore free calcium rapidly, leading to the reduced thrombocytopenia as seen in his trial.

Conclusion

Vitamin D may have a role in Dengue management. A larger clinical trial is needed to further investigate the relationship between Vitamin D and dengue management.

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