Effect of Vitamin D on clinical profile of sickled children: A prospective study

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ABSTRACT

Background: Vitamin D status in sickle cell children (SC) has been widely discussed and its effect on clinical profile among SC is currently highly debatable. **Objective:** The objective of this study was to determine the clinical outcomes in terms of morbidities for Vitamin D supplementation among Vitamin D deficiency (VDD) SC. **Materials and Methods:** A total of 428 children as per predefined inclusion and exclusion criteria were enrolled in this present prospective study, after receiving written informed parental consent. Patients were supplemented with Vitamin D according to their serum status and followed up at 3 subsequent visits (0, 6, and 12 weeks). All the relevant statistics were done by SPSS v 25.0 (IBM, New York). **Results:** A total of 428 diagnosed cases of sickle cell anemia were enrolled, from which 272 (63.6%) were male and 156 (36.4%) were female, and 393 cases were found to be VDD (92%). The mean age of the study population was 88.39 (46.27) months. Vitamin D supplementation was significantly associated with decrease in number of vaso-occlusive crisis, duration of hospitalization, and duration of pain hours ($p<0.05$). **Conclusion:** Vitamin D supplementation among sickled children with Vitamin D deficiency has a positive effect on its clinical parameters.

Key words: *Duration of hospitalizations, Duration of pain hours, Number of vaso-occlusive crisis, Prospective study, Sickle cell anemia, Vitamin D*

Sickle cell disease (SCD) is a hemolytic disorder with clinical manifestations which result due to mutation on the beta-globin genes that generate an abnormal hemoglobin product (HbS) within the red blood cell (RBC) [1,2]. During the periods of hypoxemia and deoxygenation, conformational change in HbS results in the deformation of RBCs into a "sickle" shape that leads to vaso-occlusion and exaggerated hemolysis, which, in turn, causes chronic anemia [3].

Individuals with SCD suffer global deficits in energy and nutrients intake, with increased catabolism that ultimately causes multiple macro- and micronutritional deficiencies [4,5]. Among the micronutrient deficiencies, Vitamin D deficiency (VDD) is common in people with SCD, regardless of age and season. The prevalence of VDD among individuals with SCD ranges from 33% to 100% [6]. There is a decrease in pain symptoms and analgesic use with Vitamin D supplementation among sickled children [7]. Since Vitamin D regulates the absorption and excretion of calcium and is essential for bone mineralization, its deficiency in people with SCD may contribute to the myriad of musculoskeletal health problems such as muscle weakness, chronic debilitating bone pain, vascular necrosis, bone fragility, and compression fractures, which, in turn, can lead to functional impairment in mobility and can interfere in education, employment, and psychosocial development [8,9].

However, the literature on the association of Vitamin D supplementation with the requirement of a number of units of blood transfusion (BT), number, frequency, and duration of hospitalization is scarce. According to a statement in 2015, 5.35 lakh of the population of Odisha was affected by the disease [10]. Thus, the present research proposal has been designed to determine the short-term clinical outcomes in terms of morbidity for Vitamin D supplementation among VDD sickled children.

MATERIALS AND METHODS

This present prospective observational study was conducted in a tertiary care teaching hospital of Western Odisha from November 2017 to October 2019 after approval from the Institutional Ethical Committee. High-performance liquid chromatography confirmed sickle cell homozygous children (HbSS) under 14 years of age, of either gender attending outpatient department (OPD), inpatient department (IPD), and sickle cell center of our institute was enrolled in the study after receiving proper written informed consent from their parents or legal heir.

Critically ill children, splenectomized children, children with hypercalcemia and hypervitaminosis D, who had received calcium, Vitamin D supplement, lipid-lowering drugs, digoxin, and thiazide diuretics during the past 6 months, having

pre-existing diseases such as chronic liver or kidney diseases, and parathyroid disorders were excluded from the study. Based on a previous study [11], taking absolute precision as 5% and confidence interval of 95%, the minimum required sample size was calculated by a single proportion absolute precision method (n master v 2.0, BRTC, Vellore) to be 420 after adjusting for correction factor and attrition. Out of 6348 SCD patients attending our hospital, applying a systematic random sampling technique (sampling interval of 15), 428 cases were enrolled (Fig. 1).

Serum Vitamin D was estimated by radioimmunoassay with the trade name of Diasorin machine (Beckman Coulter, Ireland) [12]. Normal serum Vitamin D value was taken as 30–100 ng/ml with <30 ng/ml declared as deficient [13]. On the basis of the status of Vitamin D level, two groups were formed (Vitamin D deficiency and normal). The deficient group was supplemented with Vitamin D as per norms [14], and all the groups were followed up to 12 weeks from their first visit to our center. The data of children from OPD, IPD, and sickle cell center were collected on daily basis with the help of nurses on duty.

The number of BT per sickled days was defined as the total number of BT till enrolment/age of the child in days till enrolment. The number of vaso-occlusive crisis (VOC) per sickled days was defined as the total number of VOC till enrolment/age of the child in days till enrolment. The number of hospitalization per sickled days was defined as a total number of hospitalization/age of the child in days till enrolment. Duration of hospitalization per sickled days was defined as a total duration of hospitalization in number of days/age of the child in days till enrolment. Duration of pain hour per sickled days was defined as the duration of VOC in the hour/age of the child in days till enrolment.

All the relevant data were collected in a predesigned case report format. Data validation and data cleaning were done manually by two separate persons not involved in the study. Continuous data were expressed in mean (SD) and categorical data were expressed in proportions. Data normalcy testing of continuous data was done by the Shapiro–Wilk test and no transformation was required. All the descriptive, inferential, and longitudinal analyses were done by SPSS v 25 (IBM, New York, USA). For all statistical purposes, $p<0.05$ was considered statistically significant.

Table 1: Baseline variables of the study participants

Baseline variables	Mean (SD)
Serum 25-OH Vitamin D* in ng/ml	19.00 (5.95)
Number of BT per sickle days	0.020 (0.01)
Number of VOC per sickle days	0.043 (0.020)
Number of hospitalization per sickled days	0.06 (0.03)
Days of hospitalization per sickled days	0.18 (0.12)
Hours of pain per sickle days	0.42 (0.21)

*25-hydroxyvitamin D, BT: Blood transfusion, VOC: Vaso-occlusive crisis

RESULTS

A total of 428 diagnosed cases of sickle cell anemia were enrolled, out of which 272 (63.5%) were male and 156 (36.5%) female. The mean age of the study population was 88.39 (46.27) months. A total of 393 cases were found to be VDD (92%), out of which 63.3% were male and 36.7% were female. The baseline variables of the study participants were analyzed (Table 1). There was no significant change in mean of number of BT and mean of number of hospitalization per sickled days for 12 weeks among VDD children as compared to normal Vitamin D level ($p=0.191$ and 0.584, respectively). The mean of the number of VOC, duration of hospitalization, and duration of pain hour per sickled days were significantly decreased for 12 weeks among VDD children as compared to normal Vitamin D group ($p<0.001$, 0.009, and <0.001, respectively). The longitudinal analysis of variables for 12 weeks was done (Table 2).

DISCUSSION

In the present study, we found that VDD was 92% among sickle cell children, and most of them were male. Supplementation among VDD group resulted in a lesser number of VOC, duration of hospitalization, and pain hours. However, the number of BTs and hospitalizations did not change clinically.

The male preponderance of VDD (63.3%) in the present study is not in accordance with a prior study done in Saudi Arabia by Hussain *et al*. [15]. The cause of this discrepancy may be due to the male predominance in our region, ethnicity, and enrolment of more male children during the study period. The number of BT did not change even after the supplementation of Vitamin D to deficient group, which may be due to the effect of hydroxyurea, as all the study participants were taking the same irrespective of their Vitamin D status [16]. Change in number of hospitalization could not be correlated with Vitamin D supplementation for 12 weeks. There are currently no studies on this effect.

The number of VOC per sickle days and duration of hospitalization per sickle days were significantly decreased for 12 weeks. These results were in accordance with the study done in 2018 by McCaskill *et al*.

Table 2: Longitudinal analysis of variables for 12 weeks after adjusting for correction factor

Incidences per sickled days	Mean (SD) at 0 week	Mean (SD) at 6 weeks	Mean (SD) at 12 weeks	Epsilon (€)	Greenhouse–Geisser correction	p-value*
Serum 25-OH Vitamin D in ng/ml	18.05 (4.81)	18.78 (4.72)	19.32 (4.76)	0.073	32.774	0.001*
Blood transfusion	0.02 (0.01)	0.02 (0.01)	0.02 (0.01)	0.004	1.700	0.191
Vaso-occlusive crisis	0.04 (0.02)	0.04 (0.02)	0.04 (0.02)	0.053	23.421	0.001*
Number of hospitalization	0.06 (0.03)	0.06 (0.03)	0.05 (0.04)	0.001	0.308	0.584
Duration of hospitalization (days)	0.18 (0.12)	0.16 (0.13)	0.16 (0.12)	0.016	6.792	0.009*
Duration of pain (h)	0.43 (0.22)	0.42 (0.21)	0.41 (0.21)	0.058	25.898	0.001*

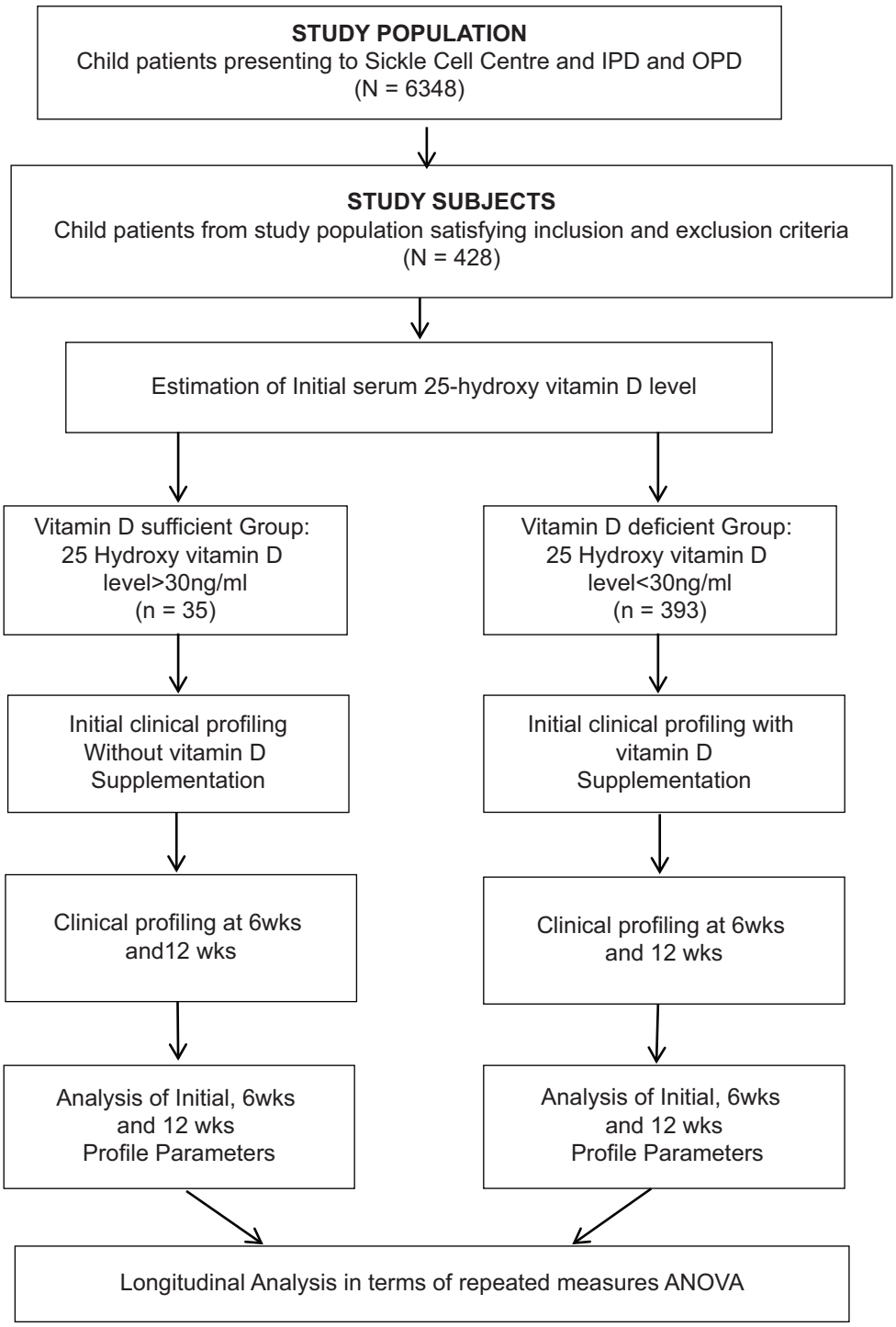

Figure 1: Study flowchart

who found that SCD patients receiving Vitamin D supplementation had less SCD-related hospitalizations when compared to patients who did not receive the supplementation [17]. In the present study, there was a significant decrease in pain hours among the Vitamin D supplemented group as compared to non-deficient group. This is supported by a few similar studies done by Soe *et al*., in 2017 [7], and Osunkwo *et al*., in 2011 [18], who found a decrease in pain symptoms and analgesic use with Vitamin D supplementation. This may be due to the fact that Vitamin D decreases the release of mediators of inflammation and SCD being an inflammatory process; there is a decrease in pain symptoms.

Our study is one of the rare studies done on the effect of Vitamin D in SCD; however, there were a few limitations. The inclusion of only steady-state sickle patients could have yielded more reliable results. There were increased chances of bias in the study such as recall bias, information bias, or reporting bias.

CONCLUSION

Large multicentric trials are required to determine the efficacy and safety of Vitamin D supplementation among sickled children. Long-term follow-up is required to address the complications, if any.

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