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Impact of Vitamin D Supplementation on Pain Management in Sickle Cell Disease Patients

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Abstract

Background: Vitamin D deficiency is prevalent among patients with sickle cell disease, regardless of their age or the season. Since there has been no extensive research on the impact of vitamin D on pain in sickle cell disease, this study aimed to evaluate how vitamin D supplementation influences pain management in these patients.

Materials and Methods: This retrospective study was conducted on children (12.3±4.45 years old) with definitive diagnosis of sickle cell. The study was done in the Department of Oncology of Shahid Sadoughi Hospital, Yazd, Iran, over the years 2019-2021. Thirty patients (14 boys and 16 girls) with vitamin D insufficiency and deficiency entered the study and 50000 IU vitamin D was given weekly for 16 weeks. The measurement of vitamin 25(OH) D3 before and after intervention was done by ELISA method (Monobind kit, USA). Pain intensity assessment was also done. Other relevant data were extracted from the patients' medical records.

Results: In this study, amomg 30 patients, 46.6% of them had vitamin D deficiency. A significant reduction in pain intensity was observed in patients following the intervention ($p<0.05$).

Conclusion: Based on the findings of this study, vitamin D was effective in reducing pain intensity in these patients. Therefore, vitamin D can be used in the pain management of these patients.

Keywords: Pain, Sickle cell disease, Vitamin D supplementation

Introduction

Sickle cell disease (SCD) is a hereditary disorder of red blood cells characterized by its pro-inflammatory nature and impacts millions of individuals worldwide (1). The manifestation of sickle cell illness occurs due to mutations in the β-globin genes which generate abnormal hemoglobin, called hemoglobin S, in the red blood cell (2). When hemoglobin S, or sickle hemoglobin, becomes deoxygenated, the substitution of β6 glutamic acid with valine causes hydrophobic interactions with other hemoglobin molecules, leading to the formation of large polymer aggregates (3). The polymerization of this molecule is the initial step in the molecular pathogenesis of SCD, leading to red cell distortion (3).

In this condition, red blood cells take on a crescent shape, become rigid, and obstruct small blood vessels, preventing sufficient oxygen from reaching tissues and organs (2). This blockage can lead to pain, acute chest syndrome, stroke, and short- and long-term organ damage (2). The most common reasons for seeking medical treatment by individuals with SCD are musculoskeletal and pain complications (2). Chronic bone problems, including avascular necrosis, osteopenia, osteoporosis, and chronic arthritis are also common in individuals with SCD (4). Additionally, due to increased catabolism and insufficient energy and nutrient intake, individuals with SCD often experience various micro- and macronutrient

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deficiencies, including vitamin D deficiency (1). In children, vitamin D deficiency is defined as a 25(OH) D level below 20 ng/mL, insufficiency as 20–30 ng/mL, and sufficiency as levels above 30 ng/mL. Vitamin D deficiency is prevalent among SCD patients, regardless of age or season (2). Since vitamin D plays a critical role in maintaining calcium homeostasis and supporting bone mineralization, its deficiency may exacerbate musculoskeletal issues in SCD patients (5). Although the relation between chronic pain and vitamin D has not yet been fully understood, the use of vitamin D supplementation by patients with SCD may have a dual role in alleviating the chronic pain and improving bone health (6). Despite the importance of this disease, no comprehensive study has been done on the effect of vitamin D supplementation on management of pain in patients with SCD. Therefore, this study aimed to assess the effect of vitamin D supplementation on pain management in patients with SCD.

Materials and Methods

Sample selection

This retrospective study was carried out on patients with a confirmed diagnosis of SCD in Department of Oncology of Shahid Sadoughi Hospital, Yazd, Iran, during 2019-2021.

Inclusion and exclusion criteria

Inclusion criteria were definitive diagnosis of SCD and complete medical records. Patients lacking complete medical records were excluded from the study.

Vitamin D therapy

In this step, 35 patients were selected. Among them, 7 patients (20%) had sufficient vitamin D level and did not receive supplementation and 30 patients (14 boys, and 16 girls) entered the study and 50000 IU vitamin D was given weekly for 16 weeks (7). Then, vitamin D level was measured and if it was not sufficient, the therapy continued. Moreover, if vitamin D level in serum exceeded 100 ng/mL during treatment, therapy was discontinued (7). Levels of 25(OH)D3 in human serum were assessed before and after the intervention by ELISA Kit (Monobind, USA).

Pain intensity assessment

The data were collected using the Oucher Pain scale, which is a scale for assessing the intensity of pain. The tool was first created by Beyer in 1988. It contains two scales which enables children to rate the intensity of their pain. It consists of a numerical scale, a scale with a series of numbers rating pain intensity from 0 to 100, for children who can count to 100 and a pictoral scale, a six-picture photographic scale for children who are unable to count. The pictorial scale contains six different pictures of a child's face. Responses range are from 'no pain' to 'the greatest pain' imaginable. The visual scale is a vertical representation, numbered from 0 to 100, yielding ordinal level data, while the numerical scale offers interval data (8). It is noteworthy here that in some cases, the children's parents reported the severity of their children’s pain because of the absence of the children themselves or their very young age.

Ethical Consideration

The study received ethical approval from the Ethics Committee of Shahid Sadoughi University (IR.SSU.MEDICINE.REC. 1393.79).

Statistical analysis

The collected data was subjected to SPSS Statistics 19.0 and a Chi Square test was ran for analyzing the data. Furthermore, p values less than 0.05 were assumed as significant.

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Results

The average age of patients was 12.3±4.45 years old. Table I shows the frequency of pain intensity in the two groups. As presented in Table I, a significant statistical difference in the frequency of pain intensity was noted between the two groups ($p<0.05$).

The classification of vitamin D level in the two groups (insufficiency and deficiency) is shown in Table II. As shown in Table II, the majority of atients had vitamin D insufficiency.

In addition, the number of hospitalization was decreased after intervention.

Table I: The intensity of pain in the two groups

The intensity of pain	Before intervention Number (%)	After intervention Number (%)	p value
No pain	1 (3.3)	5 (16.7)	0.032
Mild pain	6 (20)	13 (43.3)	
Moderate pain	7 (23.4)	3 (10)	
Severe and very severe pain	16 (53.3)	9 (30)	
Total	30 (100)	30 (100)	

Table II: The vitamin D level

Vitamin D level	Before intervention Number (frequency)
Deficiency	14 (46.6)
Insufficiency	16 (53.4)
Total	30 (100)

Discussion

Different incidence of vitamin D in individuals was due to different mechanisms, including the reduced synthesis of vitamin D in the skin due to increased melanin and differences in diet (9-11). Vitamin D, 25(OH) D, deficiency levels (<20 ng/mL or 50 nmol/L) (7) is one of the most common nutritional problems among individuals with SCD (12, 13, 14). SCD can lead to damage to the intestinal mucosa, and thus inability to absorb nutrients (9, 15), increased basal metabolic rate, and higher demands for nutrition to retain normal physiologic function. All of these can contribute to Vitamin D deficiency (9). Vitamin D deficiency can be treated reliably and inexpensively. Treating vitamin D deficiency can potentially improve health outcomes among individuals with SCD (9). In this study, 46.6% of the patients were found to be vitamin D deficient, while 20% had sufficient vitamin D levels. Similarly, Anna Hood et al. reported that 45% of their patients were vitamin D deficient and 20% had adequate levels, aligning with the findings of this study. In contrast, Han et al. observed that 69% of their patients had vitamin D deficiency, which is higher than the results reported here. The main objective of vitamin D supplementation for SCD patients in this study was to sustain serum 25(OH) D levels at or above 30 ng/mL (($\geq$ 50 nmol/L). The findings indicated a significant reduction in pain intensity management before and after vitamin D treatment, along with a notable

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decrease in hospitalizations post-treatment (14). Additionally, Osunkwo et al. found that lower serum levels of 25 (OH) D were linked to chronic pain (6). Walter et al. conducted a comparison between individuals with vitamin D deficiency and those without, finding a significant difference in the mean pain and discomfort scores between the two groups (16). Their results are consistent with the results of this study. Hann et al. reported that vitamin D deficiency was related to acute and chronic pain in patients with SCD (14). This is in line with the finding of this study. The researchers also reported that the use of high dose oral ergocalciferol by patients with SCD with vitamin D deficiency was effective in restoring 25(OH) D levels in these patients (14). Soe et al. examined the impact of vitamin D supplementation in SCD patients and observed that it raised serum 25(OH) D levels. After 8 weeks, the group receiving vitamin D experienced fewer pain days compared to the placebo group. They also compared two oral vitamin D doses (100,000 IU/month and 12,000 IU/month) and found that the higher dose led to greater increases in serum 25(OH) D levels (2). No statistically significant difference, however, was seen between the two groups in terms of adverse events. Moreover, the two groups were not different from each other in terms of their pain or forced expiratory volume in one second (2). Lee et al. found that children with SCD exhibited lower levels of 25(OH) D and experienced acute pain (17). This is in line with the finding of this study. Another retrospective study demonstrated the association between lower level of 25(OH) D and higher opioid use in patients with SCD (18). Adewoy et al. observed that the treatment of adult patients with SCD with calcium and vitamin D could restore levels of 25(OH) D to the normal range and improve bone mineral density; however, the biomarkers of bone resorption remained unchanged (19). Other studies also showed that vitamin D could modulate inflammatory diseases, including chronic kidney disease, infection, and asthma. This finding can provide a potential mechanism for explaining how vitamin D may help to reduce acute and chronic pain in patients with SCD (6, 14, 17) and emphasizes the importance of the use of vitamin D supplementation in patients with SCD suffering from vitamin D deficiency. The precise mechanism of vitamin D for reducing pain is unclear. It is thought that vitamin D deficiency may worsen the disease progression and heighten the risk of complications by altering immune and neural processes that are associated with pain perception (7).

Conclusion

Based on these results, vitamin D was effective in reducing pain intensity in these patients with vitamin D insufficiency and vitamin D deficiency. Therefore, it seems that vitamin D can be used in the pain management of these patients.

Limitation of the study

One of the most important limitations of this study was that timing of visit in different seasons was not recorded.

Ethical considerations

The study received ethical approval from the Ethics Committee of Shahid Sadoughi University (IR.SSU.MEDICINE.REC. 1393.79).

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Authors' contributions

Ehsan Rezaeinejad conducted the study and collectec data. Azam Hashemi designed the study and edited the manuscript. Morteza Zangeneh Soroush, and Fatemeh Poorhosseini wrote the study and designed the study.

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Conflict of interest

The authors report no conflicts of interest related to this study.

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