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Pharmacological Supplements Efficacy in Management of chronic pain associated with Sickle Cell Disease: A narrative review

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REVIEW

Pharmacological Supplements Efficacy in Management of Chronic Pain Associated With Sickle Cell Disease: A Narrative Review

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Abstract

Sickle cell disease (SCD) is a hereditary ailment that can cause severe pain and suffering to people who are affected. However, with continued investment in research and treatment options, we can make progress towards improving the lives of those with SCD. Over 40% of patients experience painful vaso-occlusive crises (VOCs), so we must work towards finding solutions and providing support for those living with this condition, These episodes, a hallmark of SCD, significantly contribute to morbidity, mortality, and a diminished quality of life, while also incurring substantial healthcare costs. Chronic pain particularly affects older adolescents and adults with SCD, with over half reporting daily discomfort. Opioid-based analgesics, though still the main form of pain management, have limitations. Their effectiveness is limited, and they come with risks of adverse effects and addiction. Therefore, exploring alternative, for pain management strategies is crucial. This review dives into the potential of pharmacological supplements for this purpose. Deficiency in vitamin D is linked to increased complications in SCD. While evidence suggests vitamin D supplementation might help manage pain in SCD patients, more clinical trials are needed to confirm this benefit and determine the most effective dosage. L-arginine supplementation shows promise in reducing pain and hospital stays, while inhaled nitric oxide has yielded mixed results. Zinc deficiency is common in SCD, and supplementation may decrease infections, improve immunity, and reduce pain crises. Because of their anti-inflammatory qualities, omega-3 fatty acids may lessen the frequency of pain and inflammatory markers. Overall, the evidence for most supplements remains inconclusive, highlighting the need for further clinical research for promising supplements of vitamin D and omega-3, to establish definitive conclusions regarding their efficacy and safety in SCD patients. Exploring combination therapies and tailoring interventions to individual needs may hold promise for comprehensive pain management strategies.

Keywords: Chronic pain, L-arginine, Nitric oxide, Omega 3, Opioid alternatives, SCD pain, Sickle cell anemia, Supplements, Vitamin D, Zinc

1. Introduction

An inherited blood condition known as sickle cell disease (SCD) is characterized by recurring vaso-occlusive crisis (VOCs) a complex phenomenon initiated by HbS polymerization within red blood cells. Approximately 5% of the world's population is estimated to carry the mutant Hb gene [1]. The majority of the distribution worldwide is concentrated in the regions of sub-Saharan Africa, the Middle East, and India. According to reports, the region of Sub-Saharan Africa accounted for approximately 75% of newborns diagnosed with homozygous sickle cell disease on a global scale in the year 2010 [2]. This HbS polymerization not only induces misshapen red blood cells prone to blockage in small vessels but also triggers the innate immune system via plasma heme and HbS. The resulting activation of the immune system, along with increased blood cell adhesiveness, further contributes to vaso-occlusion, highlighting the interplay between abnormal red blood cell morphology and

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immune response in SCA pathogenesis [3]. These VOCs, a hallmark of SCD, manifest as several painful episodes in the year with different severity [4,5], leading to organ damage, systemic complications, and a myriad of adverse consequences. Significant morbidity, functional impairment, decreased health-related quality of life, and higher healthcare costs are all experienced by SCD patients, which ultimately raises their chance of mortality prematurely. Chronic pain, a common and debilitating aspect of SCD, significantly contributes to morbidity and mortality, particularly in older adolescents and adults [6]. Over 25% of SCD patients experience daily pain, and more than half report discomfort daily [7]. Frequent pain episodes are the leading cause of hospitalization, resulting in annual healthcare costs exceeding one billion dollars in the United States of America [8]. Effective pain management in SCD remains a significant clinical challenge. Data indicate that over half of all hospitalizations for acute pain episodes result in readmissions within one month of discharge, with nearly 16% of readmissions occurring within one week [9]. Opioid-based analgesics are commonly prescribed for SCD pain management, however, they are linked to many negative consequences, including respiratory depression, constipation, vomiting, and nausea [10], as well as the risk of addiction, withdrawal symptoms, and community stigmatization [11,12]. While non-pharmacological interventions for pain management in sickle cell disease (SCD) hold promise for reduced healthcare costs, improved quality of life, and a lower risk of addiction and adverse effects compared to opioids, their widespread adoption and optimization are hindered by a paucity of robust data on their efficacy and safety relative to traditional opioid analgesics [12]. To bridge the gap in knowledge regarding pharmacological supplements for pain management for sickle cell disease (SCD), this study assesses the current body of literature on the use of various pharmacological supplements for pain relief in patients with SCD.

2. Method

This narrative review includes studies that were published by June 2023, exploring the potential of various non-pharmacological supplements to alleviate pain related to SCD. The review mainly focused on the role of vitamin D, L-arginine, nitric oxide (NO), zinc and omega 3 in reducing SCD-related pain. To conduct the research, an extensive search was performed through NCBI PubMed and the Clinical Trials website using related keywords ((sickle cell disease) OR (Sickle cell anemia) OR (Vaso-occlusive crisis) OR (pain crisis)) AND ((vitamin D) OR (omega 3) OR (cannabinoid) OR (zinc) OR (arginine) OR (nitric oxide)) of all types from the first date of publication were included. Clinical trials.gov was explored for any registered trial using an intervention with Vitamin D, Omega3, Zinc, arginine, and nitric oxide. With primary or secondary outcomes on pain reduction or Vaso-occlusive crisis in sickle cell disease. The total articles searched from PubMed were 161 articles and the registered clinical trial was 99. After excluding the irrelevant and duplicated papers and trials finally, 22 articles and 9 clinical trials were included. All of the clinical trials involve interventions used in the management of sickle cell disease chronic pain were included in this review were summarised in Table 1.

This research did not involve any human or animal subjects, and thus, ethical approval was not required.

2.1. Vitamin D

Vitamin D deficiency (VDD) poses a significant challenge in SCD management since it can mimic the clinical presentation of SCD, particularly pain symptoms from muscles and bones. This overlap can make it difficult to distinguish between acute sickle cell pain episodes and chronic pain syndromes. Furthermore, VDD may exacerbate existing bone complications associated with SCD, creating a complex clinical picture for healthcare providers [13]. It has been observed that vitamin D deficiency exacerbates the complications of sickle cell disease patients, including hospital admissions. It is recommended to consider the possibility that addressing vitamin D deficiency may result in a reduction in certain risks [13–15]. While a previous study published in 2012 among children with sickle cell disease did not find a significant association between vitamin D levels and the rate of acute pain [16], Recent studies, for instance, have demonstrated that correcting vitamin D deficiency can have significant health benefits that can reduce vaso-occlusive complications [17] and emergency visits due to painful episodes after reaching levels of 30 ng/ml [18]. Additionally, vitamin D supplementation has been shown to reduce pro-inflammatory markers (IL-2,6,8,17 and 18) in SCD patients [19]. Several studies have found a significant correlation between vitamin D deficiency and vaso-occlusive crises (VOCs) in patients with SCD. A retrospective study of 102 patients demonstrated that low vitamin D3 levels were associated with an increase in hospital admissions due to VOCs [14]. Interestingly, the study also observed that patients with higher fish or

Table 1. Summary of key findings from supplement interventions in pain management for sickle cell disease.

Supplement	Year	size	Reference	Intervention type	intervention	Results
Vitamin D	2022	150	20	Randomized Controlled Trial	Daily 1.5 ml (2800 IU) for 10 months	Daily supplementation significantly reduced vascular inflammation and pain crises compared to standard treatment.
	2019	39	21	Randomized Controlled Trial	240,000−600,000 IU over six weeks	Negative correlation was observed between serum 25-hydroxyvitamin D Concentrations and the number of pain days experienced per week. Maintaining adequate levels associated with improved physical function. High-dose pulses improved pain and quality of life in children.
	2018	62	22	Randomized Controlled Trial	100,000 IU Vs 12,000 IU monthly	No significant difference in pain scores, but improvement in quality of life for both groups.
	2021	38	23	Randomized Controlled Trial	300,000 IU followed by 1000 IU daily	no significant improvement of quality of life, pain, hospitalization or emergency visits
L-arginine, NO	2020	227	28	meta-analysis (3 RCT)	Intravenous magnesium, L-arginine, and nitric oxide	reducing pain intensity
L-arginine	2021	68	29	Randomized Controlled Trial	Oral L-arginine-hydrochloride (100 mg/kg TID) Vs placebo	Oral supplementation led to 39% reduction in analgesic requirements and 26.5% decrease in opioid need during hospitalization compared to placebo
	2022	38	30	Randomized Controlled Trial	100 mg/kg for up to five days or till discharge	Patients receiving L-arginine showed over 50% reduction in opioid requirements and lower pain scores at discharge. However similar hospital stay
	2019	50	31	Randomized Controlled Trial	Hydroxyurea plus 500 mg daily vs hydroxyurea plus placebo	Increased nitrate plus nitrite levels by the fourth month and reduced pain.
Nitric Oxide (NO)	2011	150	33	Randomized Controlled Trial	Inhaled nitric oxide gas for up to 72 h	Showed no significant differences compared to placebo.
	2021	23	34	Randomized Controlled Trial	Inhaled NO vs placebo	Inhaled NO was effective in reducing pain scores after 4 h compared to placebo. No significant difference on opioid consumption
	2022	20	35	Randomized Controlled Trial	Inhaled NO vs placebo	No significant difference in pain scores after 4 h, but decrease in pain scores after 6 h and reduced opioid usage in the NO group.

(*continued on next page*)

Table 1. (continued)

Supplement	Year	size	Reference	Intervention type	intervention	Results
Zinc	2022	32	37	Crossover Study clinical trial	50–75 mg of elemental zinc orally daily	Long-term supplementation led to a reduction in infections and pain crises, improved immunity, and reduced hospitalization rates.
Omega-3 Fatty Acids	2011	16	40	Randomized Controlled Trial	EPA 15 mg/kg/day and DHA 10 mg/kg/day for 6 months	Significant decrease in crisis episodes, but no significant reduction in inflammatory markers.
	2022	165	20	Randomized Controlled Trial	Daily 1 g (400 mg EPA and 300 mg DHA) for 10 months Vs 1.5 ml vit D (2800 IU/7 ml) in addition to standard treatment for 10 months	Daily supplementation resulted in a greater decrease in pain scores compared to vitamin D or standard treatment alone.
	2013	128	42	Randomized Controlled Trial	277.8 mg DHA and 39 mg EPA daily for one year	Significantly lower rates of vaso-occlusive crisis, anemia, and blood transfusions compared to placebo. Improved health and quality of life.
	2001	10	43	Randomized Controlled Trial	0.1 g per kg (12% EPA and 18% DHA) per day for one year	Effectively reduced pain attacks and hospital admissions.

milk consumption, both rich sources of vitamin D, had significantly fewer emergency department visits of one and three per month respectively compared to those never consume fish and milk with average 14 and 12 day [14]. These findings suggest that a lack of vitamin D may contribute to the development of VOCs and their associated healthcare burdens.

A double-blind clinical trial involving 150 SCD patients demonstrated the potential benefits of daily supplementation with 1.5 ml (2800 IU/7 ml) of vitamin D for 10 months. Compared to the standard treatment alone, vitamin D supplementation significantly reduced vascular inflammation and pain crises [20].

In a pilot study designed to assess the effects of high-dose vitamin D supplementation in pediatric sickle cell disease (SCD), 46 subjects were enrolled, 39 of whom harbored the SS homozygous genotype. High-dose oral vitamin D (240,000 to 600,000 IU) was administered over a six-week period on a weight-adjusted basis. To mitigate the risk of severe vitamin D deficiency throughout the trial, all subjects received a daily oral maintenance dose of 500 mg calcium and 200 IU vitamin D for six months. Serum 25-hydroxyvitamin D levels were significantly elevated in the high-dose vitamin D group at weeks 8 and 16, with a trend towards continued elevation at week 24. Furthermore, a negative correlation was observed between serum 25-hydroxyvitamin D concentrations and pain frequency within the high-dose vitamin D group at week 8, suggesting a potential analgesic effect. Similar trends were observed at week 16. These findings warrant further investigation in larger, randomized controlled trials to confirm the efficacy of high-dose vitamin D supplementation in improving pain management and quality of life in pediatric SCD patients. This study also found that maintaining adequate vitamin D levels was associated with improved physical function as measured by pediatric quality of life inventory (PedsQL). These results suggest that monitoring and managing vitamin D levels may benefit patients with SCD [21]. However, another study comparing monthly doses of 100,000 IU and 12,000 IU of vitamin D found no significant difference in pain scores between the two groups, although both groups showed improvement in quality of life [22].

A recent study tested whether a large dose of vitamin D3 (300,000 IU) followed by a smaller daily dose (1000 IU) could raise 25-hydroxyvitamin D levels above 75 nmol/l in people with Sickle Cell Disease. While the bolus dose effectively achieved the desired vitamin D levels, it did not result in significant improvements in quality of life,

musculoskeletal pain, hospitalization, or emergency department visits, however, these findings may be due to the small sample size and dilution of the results [23].

Further robust clinical trials are recommended to validate these findings and establish the most effective vitamin D supplementation regimen for children and adolescents with SCD over an extended period of time.

2.2. L-arginine and nitric oxide (NO)

Nitric oxide (NO) is a naturally occurring chemical that is derived from L-arginine. It has been observed to have several health benefits, including acting as a potent vasodilator and platelet aggregation inhibitor. Furthermore, it has also been noted to play a role in the downregulation of adhesion molecules and the modulation of ischemia-reperfusion injury [24]. L-arginine, a semi-essential cationic amino acid, has limited endogenous synthesis and plays a critical role in various cellular and organ functions due to its involvement in multiple metabolic pathways. Sickle cell disease (SCD) is characterized by NO deficiency, a highly effective vasodilator [25]. Studies have shown that L-arginine treatment can enhance mitochondrial activity and reduce oxidative stress in SCD patients [26].

Sickle cell disease (SCD) is associated with a multitude of complications, including vaso-occlusive pain crises, pulmonary dysfunction, leg ulcers, and shortened lifespan. L-arginine deficiency, a contributing factor, leads to reduced nitric oxide (NO) bioavailability, which in turn causes vasoconstriction and endothelial dysfunction. Given its role in NO synthesis and potential for improved cellular health, L-arginine supplementation warrants further investigation as a therapeutic strategy to improve the well-being and life expectancy of SCD patients [27].

A recent meta-analysis of three randomized controlled trials aimed to determine the effectiveness of intravenous magnesium, L-arginine, and nitric oxide in reducing pain intensity and promoting pain relief in pediatric patients with sickle cell disease who experience acute pain crises. Although the results were inconclusive, this study is a valuable contribution to the ongoing effort to identify effective treatments for sickle cell disease-related pain, and it provides a foundation for future research in this field [28].

A clinical trial conducted on 68 children with sickle cell disease (SCD) revealed that oral arginine supplementation has the potential to reduce pain and shorten hospital stay duration. This is a promising development that could lead to more effective treatments for SCD patients. Patients in the intervention arm taking oral L-arginin 100 mg/kg three time daily, experienced a significant 39% reduction in total analgesic requirements during their hospitalization compared to the placebo group. Additionally, they exhibited a 26.5% decrease in opioid need and a notable 17.5-h reduction in the mean-time to crisis resolution. However, the time for readmission did not differ significantly between the two groups [29]. Further reinforcing the potential benefits of oral arginine supplementation in SCD, a clinical trial involving 38 patients corroborated the findings of the previous study During the trial, patients in the intervention group received L-arginine thrice daily at a dose of 100 mg/kg until discharge or for up to five days. Compared to the placebo group, patients receiving arginine exhibited a remarkable reduction in opioid requirements, exceeding 50%. Additionally, they reported lower pain scores at discharge. Interestingly, the duration of hospital stay remained similar between the two groups [30]. In a recent study conducted on a small group of 50 patients in Brazil, it was observed that the administration of L-arginine (500 mg) supplements led to an increase in nitrate plus nitrite levels by the fourth month of continuous usage, while simultaneously reducing pain [31]. It was also found that the administration of L-arginine was safe and had minimal adverse effects compared to the use of a placebo in multiple studies [29,30,32].

Several published studies have explored the potential of nitric oxide (NO) in managing pain crises associated with Sickle Cell Disease (SCD). One such study involved 150 patients in a double-blind, multicenter, and placebo-controlled setting, where the intervention group received inhaled nitric oxide gas for up to 72 h. Although the treated group showed significant increases in plasma nitrate levels, there were no notable differences between the groups regarding primary and secondary endpoints such as pain score, length of hospital stay, time to resolve the crisis, and opioid usage [33].

Findings from a recent study on 23 patients suggest that inhaling NO can be an effective method to reduce pain scores after 4 h as compared to a placebo. Although the study did not observe a statistically significant difference in opioid use, it did note a reduction in opioid consumption [34]. These findings could pave the way for new, less invasive pain management techniques that reduce the reliance on opioids. Another study conducted between 1999 and 2001 involving twenty children with SCD found no significant differences in pain scores between those who were administered and those who received a placebo after 4 h The results are

promising as they indicate a significant decrease in pain scores for one group when compared to the other, and a reduction in opioid usage after 6 h with the use of inhaled NO. Although there was no significant difference in the duration of hospital stay between the two groups, this could be an opportunity for further investigation to explore other potential benefits of the treatment [35].

2.3. Zinc (Zn)

Zinc is a crucial mineral that plays a vital role in several biological processes, such as immunity, wound healing, and DNA synthesis. However, patients with SCD have a higher risk of developing zinc deficiency due to hyperzincuria and increased zinc requirements caused by continuous hemolysis. Fortunately, with proper care and attention, it is possible to address this issue and prevent further complications [36].

In a crossover study, researchers sought to identify the benefits of long-term zinc supplementation in 32 SCD patients. The study found that zinc supplementation had a significant positive impact on patients, leading to a reduction in the risk of infections and pain crises, while also improving immunity and reducing hospitalization rates. These findings are encouraging and support the use of zinc supplementation as an effective intervention in managing SCD patients and enhancing their overall well-being [37].

2.4. Omega 3

Omega-3 fatty acids have been found to possess anti-inflammatory properties that can significantly enhance physiological function. They are known to effectively reduce oxidative stress markers and boost antioxidant defense. Moreover, there is some research that suggests that omega-3 fatty acids may act as cellular activators to help alleviate the consequences of sickle cell disease [38].

A study conducted in 2019 aimed to explore the link between omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the levels of inflammatory biomarkers. The findings of the study suggest that a higher consumption of EPA and DHA may potentially assist in mitigating the severity of SCD by impeding the activation of pro-inflammatory genes and enhancing haemoglobin levels [39].

During a six-month pilot study, researchers evaluated the efficacy of DHA and EPA supplements on 16 patients. While there was no significant reduction in inflammatory markers, the study showed a significant decrease in the number of crisis episodes [40].

In a clinical study involving 165 patients, researchers compared the effectiveness of daily use of 1000 mg omega-3 (400 mg EPA and 300 mg DHA) and 1.5 ml vitamin D (2800 IU/7 ml) in conjunction with standard treatment over a period of 10 months. The results of the study showed that the group that received vitamin D had a decrease of 3 scores on the VAS score, while the group that received omega-3 had a greater decrease of 6 scores, indicating a significant difference in effectiveness. The study concluded that omega-3 was more beneficial than either vitamin D or standard treatment alone. Furthermore, supplementing with vitamin D was found to be more effective than standard therapy alone [20]. Incorporating omega-3 and vitamin D supplements in the standard treatment for pain crises can lead to cost savings. Considering its cost-effectiveness, omega-3 supplementation is a recommended measure that can be taken to manage pain crises more efficiently [41].

A clinical study was conducted in Sudan to investigate the potential benefits of Omega-3 supplementation (277.8 mg DHA and 39 mg EPA) compared to a placebo over a period of one year. The study involved 128 participants, and the results showed that the group receiving Omega-3 supplementation had significantly lower rates of vaso-occlusive crisis, anemia, and blood transfusions compared to the placebo group. The study also revealed that the participants who received Omega-3 supplementation experienced improved health and quality of life, as demonstrated by a decrease in inpatient hospital days and school absenteeism. Omega-3 supplements can improve well-being in certain medical conditions [42].

According to a recent study, taking 0.1 g per kg per day of Omega3 (12% EPA and 18% DHA) for one year can effectively reduce the occurrence of pain attacks and hospital admissions. In fact, the number of pain episodes per year decreased from 7.8 to 3.8, which is a significant improvement. This reduction is attributed to the decrease in prothrombic activity caused by Omega3 supplementation. Therefore, including Omega3 supplements in the treatment plan can be a constructive step toward managing sickle cell disease [43].

3. Conclusion

This review takes a constructive approach by exploring the potential of pharmacological supplements in managing pain associated with SCD. While the evidence for most supplements remains

inconclusive, this presents an opportunity for further clinical research and trials especially for promising supplements such as vitamin D and omega 3, to establish their efficacy and safety in SCD patients. By exploring combination therapies and tailoring interventions to individual needs, healthcare professionals can develop more comprehensive pain management strategies for those with SCD.

4. Limitation of the study

This review highlights the potential of pharmacological supplements for sickle cell pain. The variety of supplements, outcomes, and follow-up periods make comparisons difficult. Future research with robust designs, exploring combinations, cost-effectiveness, and long-term effects is needed to guide clinical practice. While promising, more evidence is required before definitive recommendations can be made.

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Ethical approval

This review article did not involve the collection or analysis of any primary data from human or animal subjects. Therefore, ethical approval was not required.

Conflict of interest

The authors have unequivocally declared that they have no competing interests to declare.

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