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Preliminary Report on the use of Nutraceuticals in the Management of Sickle Cell Anemia

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Abstract

Background: There is growing recognition of the benefits of nutraceuticals in the management of sickle cell disease but a scarcity of reports on their use. Nutraceuticals are food or parts of food that provide medical or health benefits. They include botanicals, functional foods and medicinal foods. This is a preliminary report on the use of nutraceuticals in the management of a small cohort of children with sickle cell disease in Nigeria.

Methods: Children, aged 1 to 12 years, presenting with sickle cell anemia were evaluated at baseline and at six month after the commencement of a cocktail of nutraceuticals using an objective grading tool. Changes in weight, hematocrit and frequency of sickle cell crises were determined.

Results: Ten children with sickle cell anemia were placed on nutraceuticals therapy. The average age of the children was 7.4 (range 2-12) years. Aroga immune support was the commonest component of the neutraceutical cocktail given to the children. There was a rise in mean weight (from 21.8 ± 8.9 to 23.0 ± 8.3) and hematocrit (from 22.8 ± 3.9 to 27.2 ± 3.9) at six months compared to values obtained at baseline. There was also a fall in the mean frequency of sickle cell crises at six months compared to values obtained at baseline (from 7.4 ± 6.1 to 3.2 ± 2.8). Overall, eight out of the ten children showed moderate to good clinical improvement. There was no documentation of any adverse reaction to the medications in any of the children.

Conclusion: The results suggest that the use of nutraceuticals may be beneficial in the management of sickle cell anemia in children. However, there is a need for controlled clinical trials for stronger evidence. Such clinical trials of unconventional therapies should be conducted with great care and concern for the safety of the participants.

Keywords: Neutraceuticals; Sickle cell anemia; Clinical score; Aroga immune support; Nigeria

Introduction

Nigeria, being the most populous black nation in the world, bears its greatest burden of sickle cell disease in sub-Saharan Africa [1]. Sickle cell disease is a genetically inherited condition in which the "SS" individual possesses an abnormal beta globin gene. A single base substitution in the gene encoding the human beta globin subunit results in replacement of beta 6 glutamic acid by valine, leading to the clinical manifestations of sickle cell disease. This substitution causes a reduction in the solubility of sickle cell Hemoglobin (HbS) when deoxygenated. Sickle cell disease is associated with hemolytic anemia, significant chronic end-organ damage, and early death [2]. They are also susceptible to any of the different types of sickle cell crises (Table 1).

Sickle Cell Crisis	Description
Vaso-occlusive	Acute unifocal or multi-focal painful crises, often with a drop in hematocrit level, commonly treated with rehydration and analgesics.
Splenic sequestration	Acute, painful, enlargement of the spleen caused by intrasplenic trapping of red cells resulting in precipitous fall in hemoglobin levels. Management is supportive and may require blood transfusion.
Hemolytic	Acute accelerated drop in hemoglobin level often precipitated by parasitic or bacterial infections. Commonly accompanied by fever. Management is supportive and may require blood transfusion.
Aplastic	Acute worsening of patients' baseline anemia, producing worsened pallor, fast heart rate, and fatigue. Management is supportive and may require blood transfusion. May present with vaso-occlusive crises.
Acute chest syndrome	Tachypnoea, chest pain, fever, hypoxemia, with chest findings on x-ray pulmonary infiltrates of local abnormalities.

Table 1: Simplified description of sickle cell crises used for the determination of frequency of crisis.

A major goal of management of the disease is to reduce the frequency of acute co-morbidities, sickle cell crises, and to ameliorate chronic complications like anemia, kidney disease, and cardiovascular

changes that negatively impinge on the quality of life of those living with the disease.

Conventional treatment of sickle cell anemia includes use of hydroxyurea, folic acid, amino acids supplementation, penicillin prophylaxis, and antimalarial prophylaxis to manage the condition and blood transfusions to stabilize the patient's hemoglobin level. These are quite expensive and have attendant risk factors [3]. The need to explore alternative therapies in people with sickle cell anemia has always been imperative. Nutraceuticals are food or parts of food that provide medical or health benefits. They include botanicals, functional foods and medicinal foods.

There is growing recognition of beneficial effects of nutritional factors and nutraceuticals in the management of debilitating chronic diseases [4,5]. A Nutraceutical is a fortified food product that not only supplements the diet but also assists in treatment or prevention of disease. The role of nutraceuticals in ameliorating the clinical complications of sickle cell disease is being evaluated in humans and animal models. Wandersee and colleagues in 2015 reported that Docosahexaenoic Acid (DHA) supplementation improves RBC flexibility and reduces irreversibly sickled cells by 40% in SS mice [6]. They concluded that the results point to potential therapeutic benefits of dietary omega-3 fatty acids in Sickle Cell Disease. Docosahexaenoic acid is an omega-3 fatty acid found in many water fish, including mackerel, herring, tuna, halibut, salmon, cod liver, and whale blubber. The fatty acid is commonly used for the treatment of heart disease and high blood cholesterol. It is also used for boosting memory and thinking skills, for aiding infant and child development, for certain eye disorders, and many other conditions [7]. However, there is insufficient scientific evidence to support these uses. In another study, the effects of omega-3 (n-3) fatty acid supplementation in patients with sickle cell anemia was evaluated in a randomized, double-blind, placebo-controlled trial [8]. The findings of the trial suggest that omega-3 fatty acids can be an effective, safe, and affordable therapy for sickle cell anemia. Several other studies have continued to suggest beneficial effects of Nutraceuticals in the management of sickle cell disease [9-11].

Despite increasing claims to the beneficial effects in sickle cell disease, objective evaluation of nutraceuticals use remains low, especially in developing countries where they are most likely to offer economic advantages in the management of the disease. In Nigeria, use of nutraceuticals in sickle cell disease is almost unexplored. While they continue to play an unregulated secondary role in the management of sickle cell disease, objective scientific evaluation remains scarce. There is thus a need for the development of objective methods useful in the clinical evaluation of the effects of nutraceuticals use in patients with sickle cell disease in developing countries. Here we report some preliminary findings in a small cohort of children with sickle cell disease using a simple, but objective, scoring method for their clinical follow-up and assessment. It is our belief that this guarded approach will add to growing evidence of the beneficial roles of nutraceuticals in the management of sickle cell anemia especially is sub-Saharan Africa.

Materials and Methods

Study site and demographic details

This was an observational study of clinical outcomes in a small group of children in whom the option of nutraceuticals was used in their management. Children presenting with sickle cell disease were evaluated for baseline (before commencement of therapy) and changes in clinical profiles during therapy with nutraceuticals at our medical Centre. The period of evaluation spanned through January 2016 to October 2019. Demographic details of the children were determined at baseline and at an interval of six months after the commencement of nutraceuticals therapy. The ages of the children evaluated were 1 to 12 years. At presentation, detailed clinical examination and relevant investigations (Complete blood count, renal function tests, and liver function tests) were done. Where patients present with features related to the lungs, chest x-rays and other imaging modalities as required were done. For this study, children with co-morbidities were exempted from participation so as to limit confounding factors at this preliminary phase of the evaluations.

Sickle cell crises

Guardians were asked about the frequency of occurrence of sickle cell crisis (vaso-occlusive, aplastic, splenic, acute chest syndrome, and hemolytic) in the six months prior to presentation. Descriptions of crises are as shown in Table 1. Other complications of the disease not described in the table were not used for the scoring. Any acute worsening of participants' baseline clinical condition requiring hospital care and fitting into any of the crises described was considered a sickle cell crisis.

Determination of individual clinical profiles

As briefly mentioned above, the clinical profiles of the children were determined at presentation and repeated six months after commencement of Nutraceutical therapy. This was done using a simple clinical scoring method designed for the study (Tables 1 and 2).

Clinical profile score
A. Weight Score
Did not gain/lost weight=0
Gained 0.1 to 2 kg=1
Gained 2.1 to 3 kg=2
gained >3 kg=3
B. Hematocrit (PCV) Score

No rise in/reduced PCV=0
0–5% increase in PCV=1
>5-10% increase in PCV=2
>10% increase in PCV=3
C. Sickle Cell Crisis Score
>3 in six months=0
3 in six months=1
2 in six months=2
1 in six months=3
None=4

Table 2: Clinical scale comparing baseline and sixth-month clinical profiles used for the scoring of the children with sickle cell disease.

Scores were computed based on weight at presentation, hematocrit at presentation, and estimates of frequency of sickle cell crisis in the last six months. The scores for changes in weight, hematocrit (PCV), and sickle cell crises were computed after six months of therapy. Summated clinical profiles scores were determined by adding scores for weight, pcv, and crises at for each child. Mean values of weight, PCV, and crises were determined at baseline and six months for the group of children evaluated. Mean summated clinical profile score was determined by adding the mean profile values for weight, PCV, and crises. The scores were interpreted based on the categories shown in (Table 3).

Clinical profile	Score	Interpretation
Poor	00-02	Little or no clinical improvement
Moderate	03-06	Moderate clinical improvement
Good	07-10	Good clinical improvement

Table 3: Categories of clinical profiles from summated clinical profile scores of the children.

The minimum and maximum cumulative scores from the categories in table 3 were 0 and 13 respectively. Clinical profile was categorized as poor, moderate, or good as shown in the table. A score of poor category will result from no changes in weight, PCV, or frequency of crises. Poor category will also result from further weight loss, fall in hematocrit (PCV), and increase in the frequency of sickle cell crises. Improvements in weight, PCV, and frequency of crises will result in a child being considered as having a moderate or good clinical profile at the sixth month evaluation.

Student T-test was used to determine the similarity between the mean values of weight, PCV, and crises obtained at enrolment and six months. A p-value greater or equal to 0.05 (at 95% confidence interval) was considered as no difference between the values at enrolment and six months.

Neutraceuticals and adjuvant medications

Administered nutraceuticals used by the participants during the study period were documented in the case record forms. Nutraceuticals made available for the study were Purebody, Aroga immune support, Immunaloe, Aroga Gastro-Intestinal (GIT) support, Aroga endocrine support, Alovea Aloe Vera Immune support, Aroga Brain and nerve support, Mycrohydrin, and Vitamin D. Other medications received alongside prescribed nutraceuticals were also carefully documented and considered as adjuvant medications.

Ethical considerations

This was a retrospective audit of case notes of patients attended to at our medical centre. All the children that presented with sickle cell disease were routinely followed up weekly or monthly depending on their clinical presentations and profiles. The clinical findings at six months after the baseline assessment were done. All patients' specific data are excluded from this report. Verbal consent to allow the clinical data of the children to be used for publication, with identifiers removed, was obtained from guardians.

Results

Ten children with sickle cell disease were placed on nutraceuticals therapy. The average age of the children was 7.4 (range 2-12) years. The average weight of the children at presentation was 21.8 (range 7.2-32) kg. Each of the children evaluated received a multiplex of neutraceuticals as shown in Table 4.

Initials	Age (years)	Gender	Neutraceuticals used	Adjuvant therapy
BA	5	Female	Purebody, Aroga immune support, Immunaloe, and Aroga gastrointestinal support	Hematinics
CJ	10	Male	Aroga immune and gastrointestinal support	None
DP	9	Male	Aroga immune and endocrine support	Hematinics
EC	18	Male	Aroga immune support	Hematinics
GO	18	Male	Alovea aloe vera immune support	Hematinics, one episode of antimalarial Therapy, and zinc
IU	5	Male	Aroga immune support and endocrine support	None
OE	9	Male	Aroga immune and endocrine support	Hematinics, one episode of antimalarial therapy, and aspermin
US	10	Female	Alovea aloe vera immune support	None
VP	1	Female	Vitamin D, Aroga immune, brain and nerve, and endocrine support	Hematinics
ZM	15	Female	Alovea aloe vera immune support, microhydrin, and aroga immune support	None

Table 4: Demographic, Baseline, and Treatmentdetails of the children.

Aroga immune support was the most common component of the neutraceutical cocktail given to the children. Nine of the ten children evaluated had the neutraceutical in their mixture. Adjuvant therapies administered to the children evaluated during the period were hematinics (iron and folic acid supplements) and artemisinin-based antimalarial drugs. There was no documentation of any adverse reaction in any of the children.

There was a rise in mean weight and PCV at six months compared to values obtained at enrolment. There was also a fall in the mean frequency of sickle cell crises at six months compared to values obtained at baseline. Comparison of mean values at enrolment and at six months for changes in weight, PCV, and frequency of crises gave p-values of 0.76, 0.03, and 0.06 respectively. Individual summated clinical profile scores (indicating changes from baseline scores) showed that two out of the ten children had good clinical profiles; six had moderate while two had poor clinical profiles. The mean summated clinical profile score was 4.6 which fall into the moderate clinical profile category. Eighty percent (8/10) of the children had a score of 3 and above. These results are shown in Tables 5 and 6.'

Initials	Weight Baseline (Kg)	Weight Six months (Kg)	Weight score	PCV baseline (%)	PCV six months (%)	PCV score	Crises at Baseline	Crises at six months	Crises score
BA	26	30	3	25	30	1	6	0	4
CJ	25	25	0	15.3	15	0	3	0	4
DP	35	32	0	24	36	3	2	6	0
EC	7.2	8.7	1	23	25	1	6	6	0
GO	23	20	0	25	25	0	6	6	0
IU	30	30	0	19.5	28	2	24	0	4

OE	10	10	0	25	32	2	6	0	4
US	28	29	1	18	23	1	6	3	1
VP	14	20	3	27	30	1	9	2	2
ZM	20	25	3	26	28	1	6	0	4
Mean clinical profile scores (SD)	21.8	23	1.1	22.8	27.2	1.2	7.4	3.2	2.3
	-8.9	-8.3	-1.4	-3.9	-5.7	-0.9	-6.1	-2.8	-1.9

Table 5: Clinical profile scores at sixth month of therapy.

ZM	Summated Clinical Profile Scores	Clinical Category
BA	8	Good
CJ	4	Moderate
DP	3	Moderate
EC	2	Poor
GO	0	Poor
IU	6	Moderate
OE	6	Moderate
US	3	Moderate
VP	6	Moderate
ZM	8	Good

Table 6: Categories of clinical profiles obtained from individual summated clinical profile scores.

Discussion

Effective management of sickle cell anemia can enhance stable clinical conditions in children and adults. While reports of research into the efficacies of conventional therapies in the management of sickle cell disease are increasingly being published, there is scarcity of reports on the use of neutraceuticals. Our study showed that after six months of a cocktail of neutraceutical management in a small number of children, clinical profiles moderately improved compared to baseline scores for weight, hematocrit, and frequency of sickle cell crises. The result is in line with other reports of benefits of neutraceutical therapies in people with sickle cell disease. A pilot study by Okpala and colleagues in 2011 suggests that DHA and EPA supplements reduce the number of crisis and steady state haemolysis in sickle cell disease. The safety profiles of these agents have been evaluated in a few studies with reports of good tolerance in those using them and associated lowering of oxidative stress. Arginine supplementation has also been reported to ameliorate oxidative stress in a mouse model of sickle cell disease [12,13]. These are positive reports of the use of nutritional supplements and neutraceuticals in sickle cell disease. However, there is a need for more studies on pathophysiologic, economic, and adverse reaction profiles of neutraceuticals in the management of sickle cell disease

First-line clinical management of sickle cell anemia include, use of hydroxyurea, folic acid, amino acids supplementation, penicillin prophylaxis, and antimalarial prophylaxis to manage the condition and blood transfusions to stabilize the patient's hemoglobin level. These are quite expensive and have attendant risk factors [14]. Neutraceutical cocktails have a mixture of nutrients and different components of food believed to be beneficial for the maintenance of good health.

Aroga immune support, the most common component of the cocktail used for the children evaluated, contains various nutrients and extracts which act synergistically to enhance apoptosis and optimize immune function. By enhancing/stimulating apoptosis, defective/nonfunctioning immune cells are either repaired or destroyed (if repair is not possible) and replaced. The formulation contains vitamin C, which helps in maintaining the integrity of the immune system; a part of this action is the proliferation of phagocytes, which engulf and destroy harmful invaders. Its contents also include:

- Gum Arabic, which forms a prebiotic in the gut and helps to modulate the release of inflammatory mediators by the immune system. It also functions in maintaining the integrity of the intestinal barrier).
- Ashwagandha root powder, which studies have proven to help modulate immunity by increasing the activity of natural killer cells)
- Astragalus root powder, which has natural antibiotic actions and antioxidants that protect the body against free radicals. Most

neutraceutical containing regimens are a mix of natural compounds known to boost the immune system.

The immune system is responsible for protecting the organism from diseases. Boosters of the immune system include fruits with high content of vitamin C. Such fruits include grapefruit, oranges, clementines, lemons and limes [15]. Vitamin C is thought to increase the production of white blood cells which are central to fighting infections. Vitamin D is another supplement known to boost the immune system. Vitamin D has been reported to enhance monocyte and macrophage activities. Studies have shown that healthy levels of vitamin D may help lower the risk of respiratory infections [16,17]. Zinc is another supplement reported to enhance the immune system [18]. Zinc is essential for cell development and signal transduction. It has been reported to play an important role in the inflammatory response. Zinc also specifically protects tissue barriers in the body and helps to prevent foreign pathogens from entering the organism. A deficiency of zinc has been linked with increased risk of infections. Studies reveal that zinc supplements may protect against respiratory tract infections [19]. There is increasing evidence suggesting that supplements that boost the immune system offer protective benefits in infectious and inflammatory diseases. Thus, the evaluation of these agents in sickle cell anemia is needed especially with emerging studies on the role of the immune system in the pathogenesis of the disease.

Although sickle cell disease is caused by a single point mutation in the β-chain of the hemoglobin gene that results in the replacement of glutamic acid with valine in the hemoglobin protein, studies have demonstrated that alterations in several other genes, especially immune related genes, may be associated with the natural history of the disease [20,21]. Impaired splenic function and increased susceptibility to infections have been shown to occur in sickle cell disease. Impaired leukocyte migration, chemotaxis, and function have also been demonstrated in sickle cell disease [22]. This may partly explain the predisposition to increased infections in those with the disease. Other mechanisms that have been reported to negatively affect and impair the immune system in sickle cell disease include alterations in genetic, transcriptomic, and proteomic profiles of immune cells from SCD patients, increased number of total leukocytes, impaired leukocyte migration and function, abnormal inflammatory responses and metabolic pathways, abnormalities in inflammatory cells activity, and a host of other pathogenic changes. This multifactorial aetiopathogenesis of sickle cell disease and related complications support a multi-pronged approached targeted at ameliorating these changes. A cocktail of neutraceuticals may thus be beneficial in providing required ingredients for enhanced reactivation of the immune system. This may explain in part the results of our study which suggest some beneficial effects of neutraceutical use in the evaluated children with sickle cell anemia. However, a lot remains to be done.

Our study is limited by the small sample size, uncontrolled design, need for validation of the assessment tool, weakness in the evidence for determining clinical improvement as due to the cocktail, rather than specific components, of neutraceuticals administered. This makes it difficult to ascertain which of the agents has beneficial activity. It is our belief that this report will add to growing evidence suggesting beneficial effects of use of nutraceuticals in the management of sickle cell anemia. With increasing evidence, it will become possible to conduct clinical trials on single nutraceutical agents with more confidence on the safety and efficacy of the medications. It will also become possible to determine clinically the effects specific components of nutraceuticals on the immune system of patients with sickle cell anemia.

Many of the potential effects of supplements and nutraceuticals on the immune system have not been thoroughly studied in humans. While it can be said that the benefits of neutraceuticals in sickle cell disease remains perhaps speculative and that treatment outcomes should be interpreted in a guarded manner, our study points to a need to investigate these agents using a more systematic and controlled approach, highlighting the need for clinical trials. As briefly mentioned above, such trials should be guarded and as much as possible and conducted strictly in compliance with good ethical practices guidelines. The clinical trials should involve a restricted population of participants. They should be conducted with great care and concern for the safety of the participants. In conclusion, we have reported the use of neutraceuticals in a small population of children with sickle cell anemia. The results suggest that their use may be beneficial and that there is a need for further evaluation.

Contributions

The project was designed and conducted by Dr. David Ajibade. Dr. O.S. Michael designed the clinical profile scoring tool. Both authors wrote and approved the manuscript. Authors declare that there is no conflict of interest and that the project did not receive any external funding.

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