Efficacy of the Nutritional Supplement, EvenFlo, in the Management of Sickle Cell Disease: A Randomized Controlled Trial

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ABSTRACT

Background: In this study, we investigated if a combination of the nutraceutical supplement, EvenFlo and folic acid will be superior to the standard stand-alone use of folic acid.

Methods: We conducted a randomized double-blind, active-controlled, clinical trial. A total of 70 subjects with SCD ages 5-12 years were enrolled into the study with 35 in the intervention group and 35 in the control group; 61 completed the trial (32 from the intervention group and 29 from the control group).

Results: Participants in the intervention group were significantly less likely to experience crises compared to subjects in the control group. None of the subjects in the intervention group experienced any form of vaso-occlusive crisis (VOC) compared to 93.1% of the subjects in the controlled group. Additionally, the intervention group experienced a significantly higher increase in their hemoglobin concentration from baseline (2.92 g/dL, 95% CI [2.33, 3.51]) compared the control group (1.77 g/dL, 95% CI [1.00, 2.54]). The intervention group experienced a significantly higher increase in their mean weight from baseline (4.47 Kg, 95% CI [4.02, 4.92]) while the control group experienced a decrease (-1.05 Kg, 95% CI [-1.60, -0.51]).

Conclusions: EvenFlo is a nutritional supplement effective in the management of SCD when combined with folic acid; its beneficial effect would be useful in boosting the hemoglobin concentration and weight indices individuals with SCD as well as and in limiting the crises they suffered.

Keywords: sickle cell anemia, sickle cell disease, SCD, EvenFlo, nutraceutical supplement, randomized controlled trial, RCT.

INTRODUCTION

Sickle cell disease (SCD) is a group of red blood cell abnormalities that are inherited. The disease results from mutation in the HBB (Hemoglobin, Beta) which helps in making the beta-globin protein. Heterozygotes produce a mixture of normal hemoglobin and sickle hemoglobin. Homozygotes only produce abnormal beta chains that make sickle hemoglobin, and this results in the clinical syndrome of sickle-cell disease (Ralston et al., 2018). When the sickle hemoglobin is deoxygenated, the molecules of hemoglobin polymerize to form pseudo crystalline structures known as 'tactoids.' These distort the red cell membrane and produce characteristic sickle-shaped cells (Ralston et al., 2018).

Sickle cell disease affects millions of people worldwide and affects people from several races and groups including Hispanics, South Asians, Caucasians from southern Europe, and people from Middle Eastern countries. Altogether, over 100 million people worldwide carry the sickle cell trait (American Society of Hematology [ASH], 2017; Piel, Hay, Gupta, Weatherall, & Williams, 2013). The disease is the most predominant monogenic disorder in humans worldwide and the single most common genetic disease in the United States, affecting approximately 100,000 Americans (Centers for Disease Control and Prevention [CDC], 2019).

SCD occurs in approximately 300,000 births annually. Nigeria, the Democratic Republic of Congo

and India top the list of countries with SCD births. The vast majority of SCD births occur in sub Saharan Africa where at least 240,000 children are born with the disease every year (Piel et al., 2013; Williams, 2016). An estimated 4,500 of these children are born in Kenya (Grosse et al., 2011). Worldwide, an approximate 50-90% of children born with SCD die undiagnosed before their 5th birthday (Grosse et al., 2011; Marsh, Kamuya, & Molyneux, 2011; World Health Organization [WHO], 2010).

Once clinically diagnosed, common treatment of sickle cell disease involves patients initiating daily doses of folic acid tablets to boost their hemoglobin concentration levels even as there is not strong evidence of this (Dixit et al., 2018). Antibiotic prophylaxis (penicillin V for those not allergic) are also sometimes administered to prevent against pneumococcal infection. Other treatments include use of Hydroxyurea (Borhade & Kondamudi, 2020), and blood and bone marrow transplant (CDC, 2020).

Presentation of sickle cell disease, or sickling, is precipitated by hypoxia, acidosis, dehydration and infection. Irreversibly sickled cells have a shortened survival (normal cells last 120 days) which may result in a number of acute syndromes termed 'crises' and chronic organ damage. Vaso-occlusive crises (VOCs) are a type of several types of crises and presents with severe pain with somewhat uncommon objective clinical signs and are mostly identified through experience and subjective methods (Borhade & Kondamudi, 2020). In the US, VOCs lead to more about 197,000 ED visits and 356 million dollars spent on pain management every year (Lentz & Kautz, 2017).

Apart from the crises experienced by individuals with SCD, the disease has been shown to be associated with factors such as underweight and growth deficit, stunting, and wasting in children. Others include clinical variables such as hemoglobin concentration, disease progression, nutritional factors and the type of treatment implemented (Kazadi, Ngiyulu, Gini-Ehungu, Mbuyi-Muamba, & Aloni, 2017; Dos, De, Ivo, & Cople, 2018). Crises from SCD are generally managed by aggressive intravenous rehydration, oxygen therapy, adequate analgesia (which often requires opiates) and antibiotics (Jain, Bakshi, & Krishnamurti, 2017; Yawn & John-Sowah, 2015).

Despite the options available for the treatment of SCD, there is still a lack of reprieve from the crises experienced by SCD patients and the frequency of crises remains high among those who take the conventional drugs to prevent the crises, hence, morbidity and mortality rates of patients remains high (Grosse, et al., 2011; Piel et al., 2013; Pule & Wonkam, 2014; World Health Organization, 2010). Thus, the United Nations General Assembly on 22nd December, 2008, adopted a resolution recognizing sickle cell anemia as a public health problem (United Nation, 2009).

Given opportunities that exist to help SCD patients better manage their disease, EvenFlo nutritional supplement was developed as treatment and prevention options. The present study explored the efficacy of EvenFlo, a nutraceutical supplement, in conjunction with the traditional use of folic acid by conducting a clinical trial to test the effectiveness of combined use of these active agents.

EVENFLO

EvenFlo is a nutritional supplement formulated to help manage SCD, particularly, the crises that SCD patients suffer and associated pain. The supplement was formulated to promote bone marrow cells to enter the cell cycle and boost the production of red blood cells leading to significantly increased IL-3 secretion, and significantly inhibited IFN- γ secretion. This leads to increased hemoglobin concentration, and hematocrit (Guo & Wang, 2006; Hsu, Ho, & Lin, 1996; Liu et al., 2014). An earlier observation study conducted on EvenFlo appears to show a significant proportion of participants to have improved life style in the form of improvement of appetite, anemia, general health status, pain management, and weight management (Anicet et al., 2019).

The active components of EvenFlo that make it suitable of significantly limiting SCD crises by aiding red blood cell production leading to increased hemoglobin concentration and better weight management include atractylodes, codonopsis, corydalis, dong quai, jujube, licorice root or Szechuan lovage, poria, rehmannia root, salvia miltiorrhiza, and white peony.

Atractylodes are present in different forms including atractylenolactam, biatractylolide and atractylone. Atractylenolactam exhibits anti-inflammatory activity and has anti-inflammatory, anticoagulation and gastrointestinal repair effects (Hoang le et al., 2016; Ji, Chen & Wang, 2016; Song et al., 2017; Tang, Liao, Huang, Lin, & Wu, 2017). Biatractylolide has a neuroprotective effect on glutamate-induced injury (Zhu et al., 2017). Atractylone have anti-microbial and anti-inflammatory activities (Wu et al., 2020). Codonopsis has active ingredients that helps in the replenishment of vital energy deficiency, strengthening the immune system, improving poor gastrointestinal function, gastric ulcer and appetite and decreasing blood pressure (He et al., 2015).

Corydalis is used to treat pain, inflammation and gastrointestinal dysfunctions. It significantly alleviates the mechanical allodynia (Lee, Son & Kim, 2010). Dong Quai, also known as Tang Kuei or Angelica sinensis has blood toning and nourishing effects attributed to its vitamin B12, folic acid, folinic acid, nicotinic acid, and biotin content (DeRosa & Cupp, 1997). The herb contains Z-ligustilide which has a calming effect on the nervous system, promoting relaxation and reducing pain. The herb also promotes

hematopoiesis and can help increase blood volume after injury or surgery (Chao & Lin, 2011; Deng, et al., 2009).

Jujube is also known as *Zizyphus Lotus*. It is a tropical and subtropical plant used in nutrition, health and has antimicrobial, anti-inflammatory, hypoglycemic, antioxidant, and immunomodulatory effects (Abdoul-Azize, 2016). Licorice root (also *Szechuan lovage* or *ligusticum striatum*) is a flowering plant in the carrot family which has have therapeutic properties and is used to treat a painful swelling of the joints. It has been shown to have triterpene saponins and flavonoids as its main bioactive compounds. This agent stimulates immune responses and activates antioxidant enzymes (Yang, Yuan, Ma, Zhou, & Liu, 2016).

Poria is an extract that can help increase the indexes of phagocyte, thymus, spleen, and promotes spleen antibody production, hemolytic activity, and delayed-type hypersensitivity (Chen, Zhang, & Cheung, 2010). Rehmannia Root is a blood refresher and has anti-oxidative, anti-inflammatory and anti-apoptotic effects. It helps to regulate deficient blood patterns such as anemia, irregular menses, and uterine and postpartum bleeding (Huang et al., 2013; Yuan, Yang, Han, & Ni, 2018).

Salvia miltiorrhiza is a perennial plant with active ingredients that can cause coronary vasodilatation, suppress thromboxane formation, inhibit platelet adhesion and aggregation, and scavenge free radicals. It increases the activities of catalase, manganese superoxide dismutase, glutathione peroxidase, and coupled endothelial nitric oxide synthase. (Jiang et al., 2014; Yu et al., 2015).

White Peony (*Paeonia sterniana*) contains a unique glucoside called paeoniflorin, which calms nerves and alleviate spasm and pain (He & Dai, 2011). Working with other glucosides to make up total glucosides of peony (TGP), it has an anti-inflammatory effect and protects against oxidative damage (Wu, Pu, Yu & Li, 2015).

OBJECTIVES

The objective of this study was to investigate the efficacy of a combination of the EvenFlo nutritional supplement and the active agent, folic acid compared to folic acid alone for the management of sickle cell disease.

METHODS

Study site

This study was conducted at the Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH), Kisumu, Kenya. JOOTRH provided an ideal setting to conduct this study as it is a teaching hospital involved in medical research and houses a designated SCD Clinic, the Obama Children's Clinic, with a registered list

of sickle cell disease patients.

Population

The study population consisted of patients between ages 5 and 12 years old who were diagnosed with sickle cell anemia and were registered at the study site.

Before the initiation of the clinical trial, patients at the study site were regularly prescribed a regimen of daily folic acid and proguanil medications. The folic acid is intended to help replace depleted folate stores and reduce the symptoms of anemia. Folate was expected to lead to a decrease in symptoms of anemia and help in the prevention of hyperhomocysteinemia that may predispose to thrombotic events, which, in turn, may lead to painful episodes. Thus, folic acid was the main agent used among the participants for the management of SCD before the trial. On the other hand, the patients were prescribed proguanil to help protect them against the complications of *plasmodium falciparum* infection as a result of parasitemia. It was expected to prevent bone pain crises among patients in the event they happen to experience any crisis.

Since the goal of this trial was to investigate the effect of EvenFlo combined with folic acid versus the standard care (stand-alone use of folic acid), we decided not to withdraw their routine prophylaxis medication. More so, a significant proportion of the study population reported having two or more episodes of crises in the previous six months despite their regular care routine, hence, their qualification for participating in the study. The above baseline clinical and prophylactic medication characteristics provided the basis for trial of EvenFlo without changing the status quo.

Ethical considerations and consent

This study was approved by the Institutional Ethical Review Committee (ERC) at JOOTRH. The parents and guardians of the participants voluntarily presented them for inclusion in this study and signed informed consents. The consents included statements about the rights of the subjects, information to be collected, confidentiality and the publication of this report and any other accompanying information.

Inclusion/exclusion criteria

At the beginning of the study, an assessment tool was deployed to obtain medical history of the patients. The obtained history was combined with the records available from the hospital as well as an oral interview to screen the patients. Patients were included if they had two or more crises each month for the past 6 months, had moderate anemia as determined by a hemoglobin concentration between 6-8gm/dl and have a parent/guardian who lives with them and is responsible for transportation to and from the hospital for treatment. Patients were excluded if they had a history of transient ischemic attack or clinically overt cerebrovascular accident, undergoing treatment with blood trans-

fusion therapy, receiving erythropoietin, experiencing VOC or any other crises of SCD or if their predominate cause of pain is not SCD related. Also excluded were those requiring treatment for more than 3 days per week with non-steroidal anti-inflammatory drugs (NSAIDs), receiving chronic treatment with anticoagulants or antiplatelet drugs, diagnosed with any other concurrent disease. The subjects whose parents or legal guardians declined to sign the consent form were also excluded.

Sample size

Sample sizes were calculated using G*Power (Faul, Erdfelder, Buchner & Lang, 2009). Darbari et al. (2013) had reported that 60% of participants in a study reported having at least one vaso-occlusive crisis that required treatment within a twelve month period. With this in mind, a 40 or more percentage point decrease in vaso-occlusive crises during a study period of six months was of interest. Thus, assuming proportion of participants reporting crises in the control group and the intervention group of 60% and 20% respectively, with a two-sided significance of 0.05 and an 80% power, a minimum of 20 subjects was required per group for a total of 40 subjects for the study.

On the other hand, to estimate an appropriate sample size for hemoglobin concentration and weight, a clinically significant medium effect, defined by Cohen (1988) to be Cohen's f of 0.25 (equivalent to 0.06 partial η^2) was of interest. With two groups, measurements at 3 different points in time, 0.05 significance level, rho (ρ) of 0.25 (a conservative approach), a conservative conventional non-sphericity correction epsilon (ϵ) of 0.75 and a 80% power, a minimum of 25 subjects was required per group for a total of 50 subjects for the study. Given these estimated minimum sample sizes and the need to have a buffer in case of attrition, 70 subjects were enrolled into the study.

Procedure and subject allocation

At the point of screening, informed consents were obtained and the SCD statuses of the patients were confirmed by clinicians using a multi-parameter electrophoresis machine. After each confirmation, the clinicians obtained the subject's demographic information and scheduled their first visit.

This was a double-blind study, thus, none of the researchers, clinicians or the guardians knew the participants enrolled in either group or were taking the intervention capsules. Only the pharmacist who dispensed the capsules via randomization numbers was had knowledge of subjects' group status. Subjects were randomized in a 1:1 ratio using stratified block randomization particularly given that this was not a large clinical trial.

At the first visit, examinations were conducted and clinical information obtained. Hemoglobin concentrations were measured using a Hemoglobin testing sys-

tem. Upon all examinations and laboratory test results showing no present crises or diseases, each participant received an envelope containing the medication to be used for the next 30 days. The subjects in the intervention group received 30 capsules of Folic Acid 500 microgram (mcg) and 60 capsules of EvenFlo 500 milligram (mg). The Folic Acid was to be used once a day and the EvenFlo twice daily. Subjects in the control group received 30 capsules of Folic Acid (500 mg) to be used once a day.

Participant follow-up

Subjects were followed for six months with one visit per month. At the conclusion of the first visit, each subject was scheduled for a first follow-up visit, to occur 4 weeks following the initial visit. During each visit, subjects received additional supply of medication. The data from the initial visits were considered baseline.

When the subjects returned for each follow-up visit, their clinical information were obtained and any medical events since the previous visit were documented. Any crises or medical events that happened in-between the visits were documented by the parents and guardians and reported at the next visit.

Measurement

The primary outcome variable was vaso-occlusive crisis (VOC) as characterized by excruciating pain. These mostly include acute chest, abdominal, back and joint pains. Reported cases of yellow eyes in either group were not considered VOCs and were not included in our analysis. Hemoglobin concentration and weight index data were considered secondary outcomes. These variables are adequate to assess effects of SCD given their association with the disease (Dos, De, Ivo, & Cople, 2018; Kazadi, Ngiyulu, Gini-Ehungu, Mbuyi-Muamba, & Aloni, 2017). These variables were measured during each visit.

Quality assurance

At the end of each week during the study period, a quality assurance meeting was held with clinicians, the first author and consulting pediatrician in order to review the activities and information collected that week. This included the review of completed clinical research forms, the clinicians' examinations, decisions and the laboratory results. Clinicians gave instructions on swallowing of capsules and the first dose was taken at the hospital, in the presence of an adult guardian/parent, who was chosen as a "medication buddy" to give the capsule at the right time and as per the instructions.

Statistical analysis

Demographic characteristics, rates of VOC experienced, hemoglobin concentration levels and weight indices were compared between the participants in the intervention and control groups. The rates of vaso-

occlusive crises experienced by the two groups were compared using the two proportion Z-test. We used a two-way mixed-design Analysis of Variance (ANOVA) model to compare mean hemoglobin concentration levels and mean weights at three different time points (baseline, after 3 months and after 6 months), from the two study groups. Time was the within-subject factor and group was the between-subject factor. The assumptions of the model were examined. Statistical significance was set at $p < 0.05$ except for Box's M Tests for which we used $p < .001$ given that Hahs-Vaughn (2016) and Tabachnick & Fidell (2001) recommended ignoring the test or using smaller alpha level with unequal groups due to the test's sensitivity. Confidence intervals (CIs) were estimated with 95% certainty. Data transformation was considered in rectifying the violation of the normality assumption, however, the results did not significantly differ from those of the untransformed data; thus, the untransformed results were retained for reasons of simplicity and the robustness of the ANOVA test. Statistical analyses were performed using SPSS 24 by IBM. Graphs were produced using RStudio 1.1.463 (RStudio Team, 2015).

RESULTS

A total of 120 SCD children were screened of which 70 children meeting the age requirement of 5 to 12 years were enrolled into the study. Thirty five subjects were allocated into the treatment (envelope + standard of care) group and 35 into the control (standard of care) group. Thirty-two (91.4%) subjects in the treatment group and 29 (85.7%) in the control completed 6 months study follow-up and had complete data for analysis (Figure 1). All subjects were of African race. The baseline characteristics were similar between the two groups in terms of age, gender, weight, and hemoglobin level (Table 1).

The primary outcomes data being the amount of VOCs experienced by the subjects were compared between the two groups. With all 27 (93.1%) of the 29 subjects in the control group experiencing at least one form of crises by the end of the 6 months trial compared to none (0.0%) of the 32 subjects in the treat-

ment group, there was a significant difference in the proportion of subjects that experienced at least one VOC (proportion difference = 0.931, 95% CI = 0.93 to 1.00, $Z = 7.05$, $p < .001$). This represents a 93.1% difference in the proportions of subjects that experienced VOCs. Further analysis of the crises experienced by the subjects in the control group during the trial shows that 2 (6.9%) experienced no crises, 10 (34.5%) experienced one crisis, 14 (48.3%) experienced two crises and 3 (10.3%) experienced three crises (Table 2).

For the secondary outcome variable of hemoglobin concentration, there were no outliers, as assessed through studentized residuals. The assumption of normality was assessed using the Kolmogorov-Smirnov test. The assumption was partially violated with only four of the six subgroups of data satisfying the assumption ($p > .05$), the remaining two subgroups otherwise. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variances ($p > .05$) and homogeneity of covariances as assessed by Box's M test ($p > .001$). In testing if the variances of the differences between the related groups of the within-subject factor for all groups of the between-subjects factor are equal, Mauchly's test of sphericity indicated that the assumption of sphericity was met for the two-way interaction, $\chi^2(2) = 4.92$, $p = .086$. For the test of interaction effect, the results showed that there was a statistically significant interaction between the treatment and time, on hemoglobin level, $F(2, 118) = 4.08$, $p = .019$, partial $\eta^2 = .065$. Due to the statistically significant interaction between the treatment and time, we determined the simple main effects of group. Data are mean $\pm$ standard error. The results showed that hemoglobin concentration was statistically significantly higher in the intervention group at the end of the trial (10.67 ± 0.26 g/dL) compared to the control group (9.22 ± 0.27 g/dL), $F(1, 59) = 15.17$, $p < .001$, partial $\eta^2 = .205$ (Figure 2). The intervention group improved their mean hemoglobin concentration from baseline by 2.92 g/dL, 95% CI [2.33, 3.51] compared to 1.77 g/dL, 95% CI [1.00, 2.54]. Mean hemoglobin concentrations at the three periods considered are shown in table 3.

Also for weight, another secondary outcome variable, there were no outliers as assessed through the residuals. The assumption of normality was also

Table 1: Demographic Characteristics

Variable	Intervention Group (n=32)	Control Group (n=29)	Total (n=61)
Age (Years)			
Mean $\pm$ SD	8.5 $\pm$ 1.8	8.3 $\pm$ 2.1	8.4 $\pm$ 1.9
Min	6.0	5.0	5.0
Max	11.0	11.0	11.0
Gender			
Female n (%)	17 (53.1)	15 (51.7)	32 (52.5)
Race			
Black/African n (%)	32 (100)	29 (100)	61 (100)

Table 2: Vaso-Occlusive Crises Experienced During Clinical Trial

Number of Crises	Intervention Group	Control Group
None	32 (100.0)	29 (6.9)
One	0 (0.0)	10 (34.5)
Two	0 (0.0)	14 (48.3)
Three	0 (0.0)	3 (10.3)

*Data represent n (%)

Table 3: Estimated Marginal Means for Weight and Hemoglobin

		Hemoglobin Concentration (g/dL)	Weight (Kg)
Baseline	Intervention Group	7.8 ± 0.3	22.2 ± 0.9
	Control Group	7.5 ± 0.3	22.8 ± 0.9
3 Months	Intervention Group	8.0 ± 0.3	24.8 ± 0.9
	Control Group	7.5 ± 0.3	21.9 ± 0.9
6 Months	Intervention Group	10.7 ± 0.3	26.6 ± 1.0
	Control Group	9.2 ± 0.3	21.8 ± 0.8

*Data represent Mean ± SE.

Figure 1. CONSORT diagram for study enrollment

Figure 2.*Profile plot of hemoglobin concentration.* **Figure 3.***Profile plot of weight.*

partially violated with only the three subgroups of data from the intervention group satisfying the assumption ($p > .05$) while the three subgroups from the control violated it. There was homogeneity of variances ($p > .05$) and covariances ($p > .001$), as assessed by Levene's test of homogeneity of variances and Box's M test, respectively. Mauchly's test of sphericity showed that the assumption of sphericity was not met for the two-way interaction, $\chi^2(2) = 6.17$, $p = .046$. With this violation and the estimated value of epsilon greater than 0.75, we adopted the Huynh-Feldt correction based on the recommendations of Vieira (2017) and Girden (1992). The results of the interaction test showed that there was a statistically significant interaction between the treatment and time, on weight, $F(1.90, 112.28) = 174.98$, $p < .001$, partial $\eta^2 = .748$, $\epsilon = .952$, thus, simple main effects were determined. Data are mean $\pm$ standard error. The results showed that after 3 months, the intervention group had a mean weight (24.79 ± 0.87 Kg) statistically significantly higher than the control group (21.92 ± 0.91 Kg), $F(1, 59) = 5.17$, $p = .027$, partial $\eta^2 = .081$ (Figure 3). At the end of the 6 months trial, the intervention group had a mean weight of 26.63 ± 0.89 Kg, which was significantly higher than 21.79 ± 0.93 Kg of the control group, $F(1, 59) = 14.19$, $p < .001$, partial $\eta^2 = .194$. Within the six months of trial, the intervention group increased their mean weight from the baseline by a mean of 4.47 Kg, 95% CI [4.02, 4.92] while the control group experienced a decrease (-1.05 Kg, 95% CI [-1.60, -0.51]) in their mean weight in the same time period. Mean weight at the three time periods considered are shown in table 3.

DISCUSSION

EvenFlo is an effective agent in reducing the frequency of sickle cell disease crises as evidenced by a percentage difference of over 93.1% in the amount of individuals that experience any form of crises during the trial. While no subject experienced an episode of VOC among the treatment group for the 6 months, 93.1% of the subjects in the control group experienced at least one crises.

Evenflo is also effective in increasing the hemoglobin concentration of the blood for SCD patients. At the end of the 6 months trial period, the subjects in the intervention group had increased their hemoglobin concentration by a mean of 2.92 g/dl; this is significantly higher than 1.77 g/dl observed among those that took only folic acid. Similarly, the nutritional supplement saw the subjects in the intervention group increase their mean weight from the baseline by a mean of 4.47 Kg, while the control group experienced a decrease of 1.05 Kg in their mean weight during the trial period.

Overall, EvenFlo helps in the management of SCD by preventing VOCs due to SCD, increasing hemoglobin concentration and increasing weight; this is consistent with the findings of Anicet et al. (2019).

We imagine that EvenFlo provides a better alternative for SCD patients than some of the options previously available. For instance, hydroxyurea is commonly used to manage SCD. With the benefits derived from hydroxyurea also come the side effects of neutropenia, bone marrow suppression and mild peripheral blood cytopenia, elevation of hepatic enzymes, anorexia, nausea, vomiting and infertility (Agrawal, Patel,

Shah, Nainiwal, & Trivedi, 2013). These side effects are conspicuously absent with EvenFlo.

Side effects

A single participant in the treatment group had mild diarrhoea after initiation of treatment; the diarrhoea stopped after a couple of days and the participant continued with the treatment until the end of the study. The diarrhoea may have been a side effect of the nutritional supplement, however, the single occurrence was not sufficient to draw definitive conclusions. No other possible side effect was reported.

Limitations

A limitation of the study relates to our passive follow-up of subjects. Limitations of this approach is a reliance on the subjects and their parents/guardians to narrate any crises experienced between any two visits at the next visit, there is a possibility of not been able to capturing certain crises. A system for real-time reporting can be implemented in the future studies.

Another limitation has to do with a subjective method of measuring compliance. We relied on the parents/guardians to see to the proper use of the supplements and oral report of compliance. Some parents/guardians reported that their wards had difficulty in swallowing the capsules and we were not able to do directly the administration of the supplements but relied on parents/guardians to administer it daily). A tracking system can be provided to monitor compliance.

Additionally, the six month study period is somewhat short, a longer study period of 12 months or more can be considered in the future. Also, the impact of EvenFlo alone on SCD patients without the administration of folic acid may be explored in the future while addressing the limitations mentioned.

Furthermore, none of female subjects in this study was known to have started their monthly period yet. Given that SCD is associated with delay in menarche and gonadal dysfunction (Kopeika et al., 2019; Stimpson, Rebele, & Debaun, 2015), a study on young women and women of reproductive age may help understand the effect of this supplement on that group.

CONCLUSION

The results from this randomized controlled trial showed that EvenFlo in addition to folic acid, is an effective agent in the management of SCD. Thus, we recommend the use of EvenFlo for the management of SCD patients as its effect would be useful in significantly limiting the onset of crises suffered by these individuals as well as boosting their hemoglobin concentration and weight indices possibly leading to improved quality of lives.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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