Original Article

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A double blind, placebo controlled randomized evaluation of the efficacy of a Polyherbal Preparation (Faradin[R]) in treating sickle cell anaemia in Nigerian children

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Abstract

Introduction: The goal of management of sickle cell anaemia (SCA), for many years, has been to manage acute intermittent crises and slow down chronic end organ damage. In the past few decades, with increasing understanding of its pathophysiology, compounds primarily preventive in action are being investigated and used. Faradin® (a poly-herbal traditional supplement mixture) has been used as preventive measure against painful episodes by SCA patients as an over the counter medication and anecdotal evidence suggests that it reduced the frequency and severity of painful crises as well as transfusion requirements. Alternative medications that are both affordable and available should be considered viable alternatives provided safety and efficacy are assured because of the high disease burden in Nigeria.

Methods: This was a double controlled randomized study was carried out on twenty children. Each enrolled patient was randomized into either the herbal mixture or placebo after permission to participate in the study was obtain from the parents/guardian for children below 15 years or from both parents/guardian and the patients where the latter are older than 15 years. The main exclusion criterion was prior use or exposure to Faradin. Primary end points were pain alteration, death during study and blood transfusion frequency. Secondary endpoints were hemoglobin levels, neutrophil count, platelet count, hemoglobin F and A2 levels, serum bilirubin, nitric oxide concentration, drug toxicity and severe complications of sickle cell anemia reported during the study.

Results: There was no severe adverse event, deaths or transfusion recorded in the two groups throughout the duration of the study. Mean hematocrit was increased in the Faradin group and reticulocyte count was increased by 12 %. Faradin reduced the total white cell count to half its baseline level and increased hemoglobin F levels by 10%. Weight and appetite were reported to increased and engenders a general feeling of wellbeing.

Conclusion: Faradin appears to be an efficacious, nontoxic, available and affordable remedy for treating SCA patients in our setting.

Keywords: Faradin, polyherbal, efficacy, sickle cell, anaemia.

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Une évaluation randomisée en double aveugle, contrôlée par placebo, de l'efficacité d'une préparation à base de plantes (FaradinR) dans le traitement de l'anémie falciforme chez les enfants nigérians

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Resume

Introduction: L'objectif de la prise en charge de la drépanocytose (ACS), depuis de nombreuses années, a été de gérer les crises aiguës intermittentes et de ralentir les lésions chroniques des organes cibles. Au cours des dernières décennies, avec une compréhension croissante de sa physiopathologie, des composés principalement préventifs en action sont étudiés et utilisés. Faradin® (un mélange de suppléments traditionnels à base de plantes) a été utilisé comme mesure préventive contre les épisodes douloureux par les patients atteints d'ACS en tant que médicament en vente libre et des preuves anecdotiques suggèrent qu'il a réduit la fréquence et la gravité des crises douloureuses ainsi que les besoins en transfusion. Les médicaments alternatifs qui sont à la fois abordables et disponibles doivent être considérés comme des alternatives viables à condition que la sécurité et l'efficacité soient assurées en raison de la charge de morbidité élevée au Nigeria.

Méthodes: Il s'agissait d'une étude randomisée à double contrôle qui a été réalisée sur une vingtaine d'enfants. Chaque patient inscrit a été randomisé dans le mélange à base de plantes ou le placebo après que l'autorisation de participer à l'étude a été obtenue des parents/tuteur pour les enfants de moins de 15 ans ou des deux parents/tuteur et des patients lorsque ces derniers ont plus de 15 ans. Le principal critère d'exclusion était l'utilisation ou l'exposition antérieure au Faradin. Les critères d'évaluation principaux étaient l'altération de la douleur, le décès au cours de l'étude et la fréquence des transfusions sanguines. Les critères d'évaluation secondaires étaient les taux d'hémoglobine, la numération des neutrophiles, la numération plaquettaire, les taux d'hémoglobine F et A2, la bilirubine sérique, la concentration d'oxyde nitrique, la toxicité médicamenteuse et les complications graves de la drépanocytose signalées au cours de l'étude.

Résultats: Aucun événement indésirable grave, décès ou transfusion n'a été enregistré dans les deux groupes pendant toute la durée de l'étude. L'hématocrite moyen a augmenté dans le groupe Faradin et le nombre de réticulocytes a augmenté de 12 %. Faradin a réduit le nombre total de globules blancs à la moitié de son niveau de base et a augmenté les niveaux d'hémoglobine F de 10 %. Le poids et l'appétit ont augmenté et engendrent un sentiment général de bien-être.

Conclusion: Faradin semble être un remède efficace, non toxique, disponible et abordable pour traiter les patients atteints d'ACS dans notre contexte.

Mots clés: Faradin, poly-herbes, efficacité, drépanocytose, anémie.

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INTRODUCTION

Nigeria has the highest number of people living with both sickle cell disease (SCD) and sickle cell anemia (SCA) in the world. About 25% of the Nigerian population either has inherited the S gene as a trait, in combination with other defective hemoglobins or in the homozygous form (1). The estimated number of sickle cell infants born in the year 2010 in Nigeria is 90,000 (2). SCA has significant morbidity and high mortality in Nigeria. While studies have not been done to quantify the mortality rate attributed to SCA in the country, an estimated 50-80% of children with the disease die before their 5th birthday in Africa (3).

Clinical features of SCA begin to manifest at a time coinciding with physiological reduction of hemoglobin F level occasioned by progressive switch from fetal hemoglobin to adult hemoglobin production(4). By the age of 6 months, hemoglobin F levels taper off to reach adult levels resulting in predominance of the hemoglobin S in the homozygous phenotype. Hemoglobin S polymerizes under deoxygenated conditions resulting in damage to the red blood cell membrane causing reduced deformability of the cells (5).The red blood cells with polymerized hemoglobin S lose intracellular water, become inflexible, and abnormally adhesive (6).Consequently, they are prone to adhere to the endothelium of blood vessels, in concert with leukocytes and platelets thus impeding the flow of blood. Microvascular slugging, occlusion, ischemia, infarctions in multiple organs and hemolysis follow (7). These microvascular changes often lead to vaso-occlusive crises, hemolytic anemia, vasculo-endothelial dysfunction, progressive organ injury and early mortality.

There are cellular and genetic modifier of sickle cell disease that influence polymerization of the hemoglobin S under exposure to deoxygenation. Hemoglobin F is the most important and best-characterized genetic modifier of disease severity of SCA. It inhibits the polymerization of hemoglobin S and reduces the concentration of hemoglobin S in the red cell (8). The outcome of increased hemoglobin F concentration results in reduced frequency of acute painful crises, fewer leg ulcers, less osteonecrosis, less frequent acute chest syndromes, and reduced disease severity(9).Children with hereditary persistence of hemoglobin F generally tend to do much better clinically compared with SCA children without this genetic inheritance(9,10). Hydroxyurea increases hemoglobin F production in SCA patients and in high income countries is an important component of standard care (11). Developed originally for treating neoplastic diseases, it is known to cause myelo-suppression and consequent reduction of myeloid and erythroid cell series. Its use therefore necessitates frequent hospital visits for monitoring full blood counts an additional burden of care for limited income settings (12). It is against the performance of hydroxyurea clinically that all new medication will be measured. Other drugs being considered for treatment of sickle cell anaemia include 5hydroxymethyl-2-furfural, Aes-103, and the modified heparin drug product Sevuparin^{R}. there is however no universally acceptable drug as yet. Investigators are still searching for treatment options that could reduce morbidity, mortality and improve quality of life of SCA patients.

Another important modifier is hemoglobin A2 (13). Hemoglobin A2 levels are higher in SCA patients who have not co-inherited the β? or β^{+} gene when compared with the hemoglobin A population (14). Cellular modifiers on the other hand were identified in the Cooperative Study of Sickle Cell Disease (15).

The CSSCD has identified laboratory test results that can serve as biomarkers for clinically severe SCA. The study discovered that lower hematocrit levels and higher white cell counts are associated with a higher mortality rate. These are additional therapeutic targets of new drugs.

Hydroxyurea is costly for the average Nigerian. More cost effective and available alternatives include complementary and alternative medicine (CAM). The CAM currently used in Africa include Niprisan, Dioscovit, Nicosan, Hildi, and Faradin®. The down side to general use and acceptability of traditional medicines, by orthodox medicine, for treating SCA is the challenge posed by the inability to assess their efficacy and toxicity.

Faradin is very popular among patients attending our clinics. It is a polyherbal preparation that contains three herbal products which are *Zanthoxylum zanthoxyloides, Alnus glutinosa and Alchornea cordofolia*. The preparation was certified as fit for human consumption by the Nigerian Agency for Food and Drug Administration as supplement and has been researched upon by Nigerian Institute of Pharmaceutical Research and Development (NIPRD) that found the preparation not only to have anti-sickling, anti-oxidant and anti-bacterial

properties but also non-toxic and safe for human consumption at the recommended doses(16,17). Faradin could be useful in the prevention and treatment of bacterial infections to which SCA patients are more prone. A research team from Lagos working in laboratory mouse also found that Faradin could have antioxidant and hematinic potential.

There is yet a paucity of evidences of efficacy, safety, mechanistic questions about Faradin. These questions need to be answered scientifically for the preparation to receive endorsement for wilder use by SCA patients. The safe dosage and dosage intervals of Faradin are yet to be determined and much still has to be done to know more the mechanisms of action of the preparation.

In this study we proposed to evaluate the clinical efficacy of Faradin, explore safety and toxicity issues.

METHODS AND MATERIALS

This study was conducted at the sickle cell clinic run by the department of paediatrics at Bowen University Teaching Hospital, Ogbomoso. The sickle cell clinic has a patient load of 50 SCA patients per clinic and the clinics are run monthly. The hospital is a 500 bed capacity hospital. Twenty patients between the ages of 3 years and 17 years with a diagnosis of SCA (Haemoglobin SS) confirmed by alkaline haemoglobin electrophoresis were enrolled in the study. They were in steady state at the point of enrolment and consented to participate in the study. All participants had their diagnosis of homozygous SS disease confirmed by alkaline hemoglobin electrophoresis. All patients who were clinically unstable at recruitment or had taken hydroxyurea or Faradin at any time prior to the time of recruitment were excluded.

Randomization: The consenting patients were recruited using the simple random technique of sampling by balloting which stratified them into two groups, a placebo and a drug group. Informed consent was obtained from each parent or guardian of the subjects in cases where the subjects were less than 15 years of age. If the subject was older than 15 years of age, the informed consent was collected from both subject and parent/guardian. A pre-tested semi-structured questionnaire containing biographic and clinical information was administered. The weight of patients were measured and clinical evaluation of each patient was undertaken and findings recorded in the case report forms.

Each patient was given either Faradin or placebo depending which of the two groups they were randomised into based on the pre-prepared enveloped chosen by the patients. Both the drug and placebo were placed in identical brown bottles labelled P1 and P2 as distinguish marks the between the bottles. The drug and placebo were produced and coded by the producers and the code was not known to the study physicians and the patients and remain unbroken until after the analysis of the data had been carried out.

The drug and placebo were administered at a dose 0.20ml/kg measured out with 5ml syringes for daily dosing by each patient. Both groups were excluded from haematinics and other anti-sickling drugs throughout the study period.

Basal laboratory tests were carried out for each patient on enrolment along with their clinical parameters. Each patient was seen in the clinic monthly for 6 months. At each monthly visit, the patient was evaluated clinically and the finding are entered into the CRF while the laboratory studies were done quarterly at 1 month, 3 months and 6 months. The following samples were run: full blood count, serum bilirubin, reticulocyte count, haemoglobin F, A2 and nitric oxide.

Procedures: For the subjects aged between 3 an d 11 years of age, 5 ml of venous blood were collected from the antecubital veins after cleaning with methylated spirit. The samples were separated into three different sample bottles. Bottles one and two contained pottasium ethylene diaminetetra acetate (K EDTA) and bottle three was a plain bottle without additives. Two milliliters of blood was put in bottles 1 and 2. Full blood count was run with bottle 1 within 30 minutes of sample collection using the Cell-Dyne 1200 haematology analyser. The sample in bottle 2 was used to run Haemoglobin F and Haemoglobin A2 with high-performance liquid chromatography using Dionex UltiMate® 300 Rapid Separation LC System. One millilitre blood in sample bottle 3 was used to run total serum bilirubin. The blood was allowed to clot by standing in room temperature for 60 minutes the serum bilirubin was performed using an enzymatic colorimetric method from Randox RX Monza. The color formation was measured using the Spectrumlab 23A spectophotometer (Labomed Inc, UK) at 578nm. For the subjects aged between 13 and 17 years, 10 ml of venous blood was collected from the antecubital vein after cleaning with methylated spirit. The

samples were distributed into three different sample bottles. Bottles 1 and 2 contained pottasium ethylene diaminetetra acetate (K EDTA) and bottle 3 was a plain bottle without additives. Four point five milliliters was put in bottles 1 and 2 . The sample in bottle 1 was used immediately for full blood counts while that in bottle 2 was used to run Haemoglobin F and Haemoglobin A2 assays. One millilitre of whole blood was drawn into bottle 3 and used to run serum bilirubin (total)**.**

Data analysis: Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 23; SPSS, Chicago, IL, USA). Means of normally distributed data were obtained. Pearson's correlation coefficients were calculated to examine relationships between continuous variables. *P* values <0·05 were considered statistically significant. The Bowen University Teaching Hospital Human Research Ethical Review Committee approved this study.

Primary outcomes include pain frequency alteration, development of adverse events and deaths during the study as well as blood transfusion. Secondary outcomes include measures of haemoglobin F, A2 and neutrophil count. Other surrogate markers of response such as haemoglobin levels, mean cell volume, platelet counts, growth measured by weight gain during the study period, and any reported adverse events or toxicity. The participants, caregivers and medical coordinating staff were masked to treatment.

Definitions of adverse events were restricted to the development of acute chest syndrome, splenic sequestration and the appearance of fixed drug eruption, or rash of any description.

Acute chest syndrome: Clinical syndrome characterized by a new pulmonary infiltrate and at least three of the following: chest pain, temperature greater than 38·5°C, tachypnoea, wheezing, or cough.

Splenic sequestration: Increase in palpable spleen size by 2 cm or more below the costal margin from the last examination, accompanied by a decrease in hemoglobin of 20 g/L or more, or 20% or more from steady-state values.

RESULTS

Twenty children with SCA (HbSS) of mean age 8.6 years (range between 3-17 years) were randomly assigned to two treatment groups. Table 1 shows their baseline characteristics prior to study recruitment. 30% in the placebo groups were male compared with 50% in the Faradin group (p=0.4). The mean weight in the placebo group was 27(9.3) kg and in the Faradin group was 20.5(9.0) kg (p=0.12). table 2 shows primary outcome parameters measured in this study. We recorded no significant difference between the Faradin and placebo groups for any of the primary endpoints parameters. There was no death recorded during the study, there was no episode of transfusion required nor was there any episode of acute chest syndrome or splenic sequestration during the study in either group.

Table 3 showed the secondary endpoint parameter of the study and involved index of growth parameters, laboratory features and clinical features. No significant changes were recorded in the secondary end point parameters either. Both the hematocrit and the reticulocyte percentage rose in the Faradin group. the reticulocyte counts in the placebo group. Total white cell count fell in the two arms but the white cell count fell by 230% in the Faradin group compared to 166% in the placebo. The white cell count dropped to less than half baseline values. The platelet count fell in the Faradin group but rose in the placebo group. The nitric oxide levels fell in both arms of the study but the fall was greater in the placebo arm. There was a rise in hemoglobin A2 in the Faradin group while it remained static in the placebo arm. The hemoglobin F levels rose in both groups but the rise was higher in the Faradin group. Weight gain was noted for both treatment arms but % age gain was higher in the Faradin group. Painful episode was reduced by a half in the Faradin group while it reduced by less than a third in the placebo group. There were no adverse events recorded for any patient randomized into the Faradin arm but one patient from the placebo arm reported a mild skin rash that cleared spontaneously.

DISCUSSION

Faradin has been used for years as a food supplement by our patients at the Bowen University Teaching Hospital for many years. Most of our patients have reported obtaining benefits from the use of the preparation and we observed anecdotally that indeed they do. It is based on this observation that we resolve to engage in this study to evaluate clinically the efficacy or otherwise of the preparation.

Faradin is relatively new in medical circles; not much information is currently

available on its efficacy, toxicity, optimal dosing and adverse effects. We decided on this phase 0 study to provide answers to questions about safety and efficacy and to begin preliminary enquiries into its mechanisms of action. The study was designed as a randomized, double blind placebo controlled study in children between the ages of 3-17 years. On the subject of toxicity, there were no death nor severe adverse events following use of Faradin during the course of the study. None of the subjects taking Faradin developed a life-threatening illness (splenic or hepatic sequestration or severe infection). There were no episodes of blood transfusion in either arm but one year prior to the commencement of the study, one participant in the Faradin group required transfusion.

The one-year recall period for adverse events was chosen to minimize recall bias. The only event likened to anaphylaxis occurred in the placebo arm and not the Faradin arm. The participants presented with a mild vesicular rash restricted to the pronator surface of the forearm, which cleared spontaneously within a week. Thus, the safety and toxicity check showed that Faradin appears to be safe to administer to children within the administered dosage. The patients in the Fardin group generally showed positive features, which included a subjective feeling of well being reported more frequently compared with those on placebo. There were however no statistically significant differences between the two groups. Possible explanations for the lack of difference between the Faradin and placebo groups in terms of primary endpoints include: the relatively short duration of the study, which could have been insufficient to register changes, the small number of participants, and endpoint measurements which might not have been sensitive enough. For example, transfusion trigger in Nigeria is not universally applied due to relative scarcity of blood and self-sponsorship for medical services. It is however important to stress that at clinic reviews there were no objective evidence necessitating admissions nor was there any clinical necessity for blood transfusion. Most children with SCA do not have frequent hospitalizations for pain therefore it is not surprising that rate of hospitalization in this cohort is low (17).

The clinical and laboratory effects of Faradin were nuanced. In both the Faradin and placebo groups, there was a rise in the hematocrit of the Fardin group which was also seen in the Placebo group. The increase was greater in the Fardin group but not significantly. This is not in consonance with what was found by Akinsulie et al on ciklavit® where no appreciable increase in mean haematocrit in the patients was noted but significant increase in the controls (18). Faradin increases reticulocyte count when compared with the placebo, enhancing the response mechanisms. While the nitric oxide (a surrogate for vasculopathy) fell in both groups over the 9-month period, the fall was less in the Faradin group. Considered together, Faradin is regarded as reducing the vasculopathic effects of haemolysis and fostering a brisk compensatory response. The Cooperative Study of Sickle Cell Disease (CSSD) showed a steady state hematocrit of less than 22% was associated with increased mortality. By increasing the baseline hematocrit, Faradin could reduce mortality.

Faradin reduced the total white cell count in steady state. Leukocytosis (>15,000/mm) has been identified as a risk factor for early mortality. Leukocytosis enhances adhesive intera ctions between white cell and endothelium as increase inflammatory cytokines produced by white cells interact with endothelium ultimately causing a vasculopathy. High white cell count in SCA is also associated with greater incidence of acute chest syndrome and leg ulcers. Reduction by Faradin could provide a mortality difference.

Hemoglobin F levels were measured because it is the most reliable measure of clinical severity and risk of early death among SCA patients. Agents that increase hemoglobin F such as hydroxyurea have been shown through several studies to reduce mortality and morbidity in adults and children with SCA (19). The data suggests that Faradin increases hemoglobin F concentration. However, the increase in the hemoglobin F was observed in both the placebo and Faradin arms but while the increase was higher in the Faradin group, the difference was not statistically significant.

While Hydroxyurea is the current standard of care in high income countries, studies have however shown there is a reduced uptake of hydroxyurea in rural Nigeria for a variety of reasons. We also compared the rise of hemoglobin F in our study with hemoglobin F increase in patients on hydroxyurea in other studies. We found a wide variation in hemoglobin F levels following the use of hydroxyurea. Voskaridou et al (20) reported a 14% rise among adults while Lobo et al (21) reported a 3.2% rise among pediatric patients. Hemoglobin F levels *fell* at another study (22) exit compared to study entry. The fall was expected and attributed to physiologic changes in hemoglobin F level

during the first few years of life. In our study, the 6% rise of hemoglobin F was higher than in the study. This suggests that Faradin increased the hemoglobin F in spite of the physiologic fall in hemoglobin F during growth. High levels of hemoglobin F modify disease severity in sickle cell anaemia and are desired as also seen by imaga et al on the work on ciklavit® (23).

In this study, Faradin is observed to reduce baseline platelet count. High baseline platelet counts in SCA patients are associated with a higher incidence of avascular necrosis. A complication that affects 13% of adults with SCA and contributes to the morbidity and a reduction in the quality of life (24). If the observation in this study is affirmed, reducing baseline platelet count and maintaining the level within normal limits with the use of Faradin could reduce avascular necrosis in SCA.

Elevated HbA2 levels in patients with SCA is common with values about 0.2% - 1% higher than normal (25). Hemoglobin A2 as a non-S hemoglobin inhibits S polymerization. It may not be as efficient as hemoglobin F but, it also reduces polymerization in hemoglobin S under low oxygen tension. In our study Faradin increased the hemoglobin A2 level by 54% far higher than normal.

Nitric oxide levels decrease slightly over the course of the study from initiation to exit in Faradin group. Nitric oxide is a marker of vasodilation and is inversely correlated with vaso-occlusion. One of the effects of hydroxyurea is to promote vasodilation in SCA patients. In our study, Faradin improves vasodilation. There was weight gain noted in both treatment arms and this could be attributed to the close monitoring and enhanced nutritional education given to parents and patients by care providers. The difference in the weight gain was not of significance when Faradin is compared with the placebo but a greater improvement in appetite was reported by patients in the Faradin group which may provide an explanation for the weight gain, a welcome benefit given the fact that most SCA patients tend to be smaller and leaner than their counterparts with hemoglobin A.

At the end of the study, we concluded that Faradin seems beneficial for the general health of SCA patients. It is safe with no adverse effect and is well tolerated by the patients. Definitively has positive effects on hemoglobin F, A2, reduces white cell count and platelets but its effects on the hematocrit is inconclusive. In addition, it improves patients' appetite thus contributing to weight gain and subjectively contributes to the well-being of our cohort of pediatric SCA patients at Bowen University Teaching Hospital, Ogbomoso. Further studies with larger number of patient over a longer period will be needed to affirm the findings in this study and to evaluate further the mechanism of actions of Faradin.

Conflict of interest: The authors declare no conflict of interest.

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Table 1: Baseline characteristics of sickle cell anemia on Faradin

	Faradin N=10 mean (sd)	**Placebo N=10 Mean (sd)**
Age (years)	6.5(3.4)	10.7 (4.5)
Male	5	3
Hospitalizations in the year before the study	6	**7**
Pain events in the last year before the study	11	14
Transfusion episodes in the last year before the study	0	0
Weight (kg) at recruitment	19.8(8.4)	27.1(8.4)
Height (cm) at recruitment	110.0(20.0)	128.3(18.6)
PCV (l/l) at recruitment	24.4(4.4)	24.1(3.6)
WBC(X 10^9 /L) at recruitment	18.8(10.9)	18.3(6.0)
Platelet(X 10^9/L) at recruitment	466(220)	422(189)

Key
N- No of Patients

Table 2: comparison between entry and exit values (primary end point)

	Faradin			**Placebo**				
	N	**entry**	**exit**	**N**	**Entry**	**exit**	**T value**	**P value**
Deaths	10	0	0	10	0	0		
Acute chest syndrome	10	0	0	10	0	0		
Hospitalization	10	6	0	10	7	0		
Transfusion events	10	1	0	10	0	0		
Splenic sequestration	10	0	0	10	0	0		
Painful event	10	11	5	10	14	3	2.2	0.1

Key
N- No of Patients

Table 3: comparison between entry and exit values (secondary end points)

		Faradin			Placebo			
Laboratory values	**N**	**Entry**	**Exit**	**N**	**entry**	**Exit**	**T value**	**P value**
PCV (l/L)	10	20.7(2.0)	24.6(4.7)	10	21.6(4.3)	23.9(3.1)	0.6	0.6
WBC(X 10^9/L)	10	17.04(6.7)	7.4(4.1)	10	20.07(10.3)	12(5.1)	1.7	0.1
Platelet count(X 10^9/L)	10	484(188)	423(230)	10	404(215)	502(228)	-0.7	0.5
Reticulocyte percentage%	10	14.2(7.7)	16(9)	10	14.3(10.5)	11(7)	-0.8	0.4
Bilirubin (total)mg/dL	10	2.3(0.5)	2.0(0.4)	10	2.9(1.3)	2.3(0.4)	1.1	0.3
Nitric oxide mg/dL	10	4(2.8)	3.9(4)	10	6(3)	3(2.1)	-2.1	0.07
Hemoglobin A_2	10	3.7(0.5)	5.7(6.6)	10	3.7(.5)	3.7(.8)	0.9	0.3
Hemoglobin F	10	5.8(3.2)	6.4(3.5)	10	8.3(3.5)	9.1(3.6)	-1.9	0.08
Clinical features								
Appetite	10	Same	5(50)	10	Same	5(50)		
		Improved	5(50)		improved	4(40)		
		Reduced	0		reduced	1(10)		
Jaundice	10	Mild	4	10	Mild	4		
		Moderate	5		moderate	5		
		Nil	1		Nil	1		
Growth								
Weight(kg)	10	19.8(8.6)	21.5(9.4)	10	27.1(8.4)	29.1(8.4)	3.1	0.1

Keys
PCV- Packed cell volume
WBC- White cell count

Table 4: adverse events

	Faradin n=10 Events	**Placebo n=10 Events**
Acute chest syndrome	0	0
Hospitalization	0	0
Skin/mucosal manifestation	0	1
Splenic sequestration	0	0
Death	0	0