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Research Article

A CLINICAL STUDY ON IRON DEFICIENCY ANAEMIA WITH BIOIRON

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ABSTRACT

AIM: To assess the efficacy and safety of BioIron tablet as a herbal iron supplement for repletion in iron deficiency anaemic patients.

METHODS: Thirty subjects were evaluated in 5 sessions: screening, baseline, 14th, 28th and 56th day accompanied with a follow up assessment at least 7 days from the last visit (day 63). The efficacy parameters, such as complete blood count (CBC), red blood cell indices, erythrocyte sedimentation rate (ESR), serum iron, total iron binding capacity and serum ferritin were evaluated. Subjects were assessed using SF-36 Health Questionnaire and Fatigue Severity Scale. Safety of the investigational product was assessed by physical examination, vital signs and adverse events.

RESULTS: BioIron showed a significant efficacy in 56 days as evaluated by an increase in Haemoglobin (Hb) levels ($p \leq 0.0001$) and decrease erythrocyte sedimentation rate ($p \leq 0.001$). An increase in serum iron could be correlated to the immediate release of iron from BioIron in systemic circulation. This depicts the increased health status of subjects response to SF-36 Health Questionnaire ($p \leq 0.0001$) and decreased fatigability ($p \leq 0.0001$) assessed by Fatigue Severity Scale during the study course.

CONCLUSIONS: Without any adverse events or serious adverse events, an appreciable statistical significance has been observed with respect to Hb level, total iron binding capacity and other laboratory parameters. Hence it can be reckoned that BioIron is safe and effective for the management of IDA.

KEYWORDS: BioIron, Haemoglobin, Erythrocyte Sedimentation Rate, Ferritin, SF-36 Health Questionnaire, Fatigue Severity Scale.

INTRODUCTION

Iron deficiency anaemia (IDA) is the most ubiquitous nutritional deficiency worldwide, and is particularly prevalent in women and infants[1,2]. The processes of menstruation, pregnancy, and breast-feeding places great strains on iron stores, so that women of childbearing age most commonly suffer from low blood-iron levels. It is reported that while 3% of men present iron deficiency, around 20% of all women, and 50% of pregnant women suffer from this condition. [3]

Low iron level is one of the most addressable issues in developing countries globally. Iron in the form of heme is vital to many metabolic functions including oxygen transportation in Haemoglobin. Iron is also a component of multiple enzymes, including cytochromes, necessary for energy generation and drug metabolism. Through the donation or acceptance of an electron, iron exists in either a reduced ferrous (Fe2+) or an oxidative ferric (Fe3+) state. The majority of functional iron is contained in Haemoglobin, with smaller quantities found in myoglobin and cytochromes. [4, 5]

Iron deficiency is a very common nutritional disorder worldwide and is known to affect approximately one third of the global population. While its incidence in affluent countries is low, the incidence of IDA in India is very high. [6]

Iron deficiency anaemia (IDA) continues to be major public health problem in India. Despite being the first country to launch the National Nutritional Anaemia Prophylaxis Programme in 1970, the problem of IDA in India remains so widespread. The economic implications of IDA are also massive. The issues related to control of IDA in India are multiple. Inadequate dietary intake of iron, defective iron absorption, increased iron requirements due to repeated pregnancies and lactation, poor iron reserves at birth, timing of umbilical cord clamping, timing and type of complementary food introduction, frequency of infections in children, and excessive physiological blood loss during adolescence and pregnancy are some of the causes responsible for the high prevalence of anaemia in India. In addition, there are other multiple programmatic and organizational issues. [7]

The first line of treatment of anaemic patients is to restore Haemoglobin besides controlling iron loss and to evaluate the actual cause.

A varied array of interventions exists that are designed to prevent and correct iron deficiency anaemia. These include dietary improvement, fortification of foods with iron, iron supplementation, and other public health measures, such as helminth control. All of these approaches improve iron status in some contexts. The

appropriate use of iron supplements will be an important part of anaemia control programs in almost all contexts. [8]

Physicians are often faced with the challenge in managing iron deficiency anaemia with oral iron when a patient's iron losses exceed the maximum amount of iron that the gut is able to absorb.

Iron supplementation is generally needed to restore iron homeostasis and should be based on the degree of anaemia, underlying pathology, red blood cell count, serum iron panel, and erythrocyte morphology. These same parameters are used to monitor further iron supplementation needs. [9]

Oral iron supplements offer a more robust avenue for iron repletion. Frequently used forms of iron in supplements include ferrous and ferric iron salts, such as ferrous sulphate, ferrous gluconate, ferric citrate, and ferric sulphate[10,11]. Because of its higher solubility, ferrous iron in dietary supplements is more bioavailable than ferric iron. [11]

The bioavailability of iron from foods is ultimately determined by interactions between iron and other components in the digestive milieu. Several factors contribute to iron bioavailability such as meal composition, iron status, promoter substances (meat "factors") and metabolic demand for iron and genetic inclination for iron absorption.

BioIron tablet contains organically bound iron from green gram and BioPerine®.Mung beans technologically enriched with iron by a soil less process are the source of bioavailable iron used in BioIron tablets. Typically, mung bean contains 100-120 ppm iron. A proprietary hydroponics process is used to enrich the beans to contain 15000-17000 ppm of bioavailable iron.

BioPerine® is a standardized extract from black pepper. It contains 95% piperine. Localized thermogenic action of BioPerine® on the cells results in an increase in the rate of absorption of supplemented nutrient (s).BioPerine® may be co-administered with various nutrients for both human and animal health. [12]

A bioavailability study was conducted in two groups of rabbits – one group receiving BioIron with BioPerine® and another group receiving BioIron.

From the results, it was evident that the animals from the group receiving BioIron and BioPerine® combination tablet showed more iron bioavailability in comparison to the group receiving BioIron. [12, 13]

Based on these observations the current study was planned to assess the efficacy and safety of BioIron tablets for Iron repletion in adult male or female patients suffering with Iron deficiency anaemia.

AIMS AND OBJECTIVES

- To evaluate the clinical efficacy of BioIron tablets in the management of IDA.
- To study the adverse effects, if any, during the course of the treatment.

MATERIALS AND METHODS

PRODUCT DESCRIPTION

BioIron is a natural iron supplement from *Phaseolus aureus*. Mung beans are technologically enriched with iron by a soil less process. BioIron tablets contain bound iron from green gram and BioPerine®.

ETHICS AND INFORMED CONSENT

This trial was conducted in accordance with the clinical research guidelines established by the Drugs and Cosmetics Act, 1940, Drugs and Cosmetics Rules, 1945. Ethical Guidelines for Biomedical Research on Human Participants, 2006 of Indian Council of Medical Research (ICMR) in India, the principles enunciated in the Declaration of Helsinki (Edinburgh, 2000) and the International Conference on Harmonization (ICH) harmonized tripartite guideline regarding Good Clinical Practice (GCP). Written and oral information about the study in a language understandable by the subjects was provided. Prior to entry into the study or initiation of any study-related procedures, the subject read, signed and dated the ethics committee approved informed consent form. This study was registered at Clinical Trials Registry India under the identifier CTRI/2016/03/006744 on 21 March 2016. There were no changes to the methods or planned endpoints after study initiation.

PARTICIPANTS

Subjects were included in the study if indicated "Yes" to all of the inclusion criteria and "No" to all of the exclusion criteria.

Inclusion Criteria

1) Male and Female outpatients between 18 to 55 years.
2) Presence of iron deficiency anaemia: below normal or low Hb.
3) Using effective method of contraception, if sexually active.
4) Willing to come for regular follow-up visits.
5) Able to give written informed consent.
6) Non-use of any iron supplement for 2 weeks prior to enrolment to the study and to know the dosage timing of calcium supplement, if any.
7) Able to comply with the requirements of the protocol.

Exclusion Criteria

1) Known history of hypersensitivity to herbal extracts or dietary supplements.
2) Pregnant women, lactating women and women of child bearing potential not following adequate contraceptive measure, women who were found positive for urine pregnancy test.
3) Medical history of current haematological disorders other than iron deficiency anaemia (e.g. aplastic anaemia, megaloblastic anaemia, sideroblastic anaemia, pernicious anaemia, thalassemia, sickle cell anaemia, etc.).
4) Medical history of chronic renal disease. (5) Medical history of malabsorption syndrome, hemochromatosis.
5) Obvious internal or external bleeding as documented by medical history.
6) Medical history of hepatitis B, hepatitis C and/or exposure to HIV.
7) Participation in another clinical trial in the last 8 weeks before entry to Visit 0.
8) Evidence of alcohol or drug abuse that may, in the opinion of the Investigator, interfere with study

compliance or prevents understanding of the objectives, investigational procedures or possible consequences of the study.

9) Known or suspected hypersensitivity to iron or any of the components of Investigational Product.
10) History of any recent surgeries undergone within past 4 weeks.

TRIAL DESIGN

This non-randomized, open label, clinical trial was conducted at Life Care Hospital, Bangalore, India. Compliance with study supplement was reviewed at each visit. This was by examination of the returned supplement**.** All accountability records were incorporated into the investigator's study file. History of any medications being used currently were elicited and documented. The subjects were followed up regularly for all concomitant dosing from the time of baseline till the follow-up visit was captured and recorded. The daily food intake of the patients was recorded in the patient diaries provided to them at Visit 1 (Day 0). The same was checked and verified at subsequent visits by the investigators. The study consisted of a 56 days intervention period. Subjects met with the investigational team during screening, Day 0, Day14, Day 28, Day 56.

INTERVENTION

All enrolled subjects were asked to self-administer tablets (900 mg containing 8.5mg of elemental iron from BioIron and 2.5mg BioPerine) twice a day before food as a dietary supplement for a period of 56 days.

DATA REPORTING AND MANAGEMENT

All data were reported in the respective hospital records that were then transcribed onto the Case Report Forms (CRFs). This info entered in the CRFs were again verified by the investigators a second time. It was ensured that the source data matches with the data entered in the CRFs complying with the GCP guidelines on source verification. Data collection during this clinical study and preparation for analysis were conducted by separate and independent functional groups. Standard procedures ensured all CRFs were tracked and properly routed. The training of all the end users and clinical data management associates pertaining to the database entry and validation process was documented. The data entry operator transcribed the information from the paper CRF to the database. Validation was conducted by the data manager. The database was locked post reconciliation of all data. The locked database was provided to the statistician who was independent of the study team. The inputs were then analyzed statistically.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) software version 17.0 was used for data analysis. 'Wilcoxon signed rank sum test' was used for appropriate data set variables to reach the best possible statistical conclusion. The baseline descriptors were summarized as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables.

RESULTS AND DISCUSSION

The study was initiated only after obtaining the approval from Life Care Hospital Institutional Ethics committee. The afore mentioned ethics committee was registered under Central Drug Standard Controlled Organization (CDSCO) as per the Gazette Notification Number F.28-10/45-H (1), dated 21 DEC 1945 and last amended vide notification number G.S.R. 76 (E) dated 08 FEB 2012.

PATIENT DISPOSITION AND CHARACTERISTICS

A total of thirty patients were enrolled into the study. There were no withdrawals or dropouts in this study. Treatment compliance across various visits and overall treatment compliance for the whole study indicates that 24 (80 %) patients met 100 % treatment compliance on visit 4 (Day 56) and on an average 76.7 % met with 100 % treatment compliance during the whole study period. Demographic details of enrolled subjects were mentioned in Table 1. On the day of screening, the mean age of all the enrolled subjects was 33.7± 10.59, mean weight was 64.09 ± 14.63kgs and mean height was 153.51 ± 11.85 cm. The mean BMI was 26.7 ± 6.08 kg/m^2 with 3 males (10%) and 27 females (90%) enrolled into the study. While none of the subjects were using tobacco or alcohol. None of the enrolled subjects had abnormal medical history, except for IDA**.**

EFFICACY EVALUATION

The laboratory parameters clearly demonstrate rise in Hb levels of the subjects (Figure 1). Overall results showed a significant increase in level of Hb for all the subjects when compared from screening to day 56 with statistical significance ($p \leq 0.0001$) (Table 02).

There was increase in overall platelet count from screening to day 56, which shows almost 40% rise of platelet count in each subject on an average.

There was an increase in total leukocyte count, while there is a slight decrease in ESR over the visits, from screening through day 56**.** This indicates that BioIron not only helps increase in serum iron but also helps in decreasing the inflammation, if any. The serum iron increased from screening to final visit and the overall Iron Binding Capacity (IBC) showed a fall in the values from 452.7µg/dL to 437.3µg/dL with p value 0.015 (Figure 2). Interestingly, there was slight rise in serum ferritin from screening through day 56. The serum iron increased with p value of 0.178 from screening to day 56, with increase in serum ferritin and increase in serum iron values, it could be interpreted that the study product BioIron could have released iron quickly into the systemic circulation, thereby increasing the bioavailability of BioIron for considerable period of time.

The Short Form (SF-36) Health Questionnaire has provided significant analysis of health assessment of subjects who participated in the study. Figure 3 depicts the increase in health status, while (Figure 4) shows there is a decreased fatigability in the participated subjects. The quality of life questionnaire, SF-36 Health Questionnaire and Fatigue Severity Scale both showed statistical significance ($p \leq 0.0001$) which was performed by using "Non Parametric Wilcox on signed rank test". This indicated and showed better healthy condition of the subjects.

SAFETY EVALUATION

During the whole course of the study it was observed that none of the subjects enrolled reported any adverse events or serious adverse events. This indicates the safety of the supplement. The present clinical study data results indicate that BioIron is safe and effective for the management of IDA.

DISCUSSION:

After 56 days treatment with BioIron, significant improvement was observed in the clinical features of IDA with P value < 0.0001. Clinical features of IDA are mainly due to quantitative and qualitative reduction of Hb and less oxygen supply in the tissues. 1 gram haemoglobin, when fully saturated, combines with 1.34 mL of oxygen, therefore, haemoglobin concentration is an index of oxygen carrying capacity of blood. With the BioIron therapy, haemoglobin status improves, body tissues get adequate oxygen, body metabolism improves, and ultimately relief in clinical symptoms was observed.

The present clinical study shows the haematinic potential of BioIron. It is evident that the treatment of iron deficiency anaemia with BioIron shows statistically significant increase of hematologic values. Blood haemoglobin level was improved significantly (P<0.0001). A significant improvement in serum iron, total iron binding capacity and serum ferritin level was obtained.

As per the observations and results found in the clinical study, BioIron is an effective dietary supplement to manage IDA.

CONCLUSION

Current clinical study shows haematinic potential of BioIron with significant results for the management of IDA.

Further, subjects enrolled in this study with IDA showed an exponential increase in Hb level when compared from screening to day 56 in correction of haematological parameters. BioIron was observed to directly affect the body stores of iron. Thus, for an iron deficient individual, this preparation is beneficial in replenishing iron stores of the body. Unlike the conventional therapy, BioIron did not impart any side effects thus, claiming BioIron to be safe for internal administration.

With no abnormal laboratory values, clinical findings or changes in vital signs and with statistical significance with respect to Hb and total iron binding capacity and other laboratory parameters, it can be proposed that BioIron is effective and safe for oral consumption in the management of IDA.

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Table 1: Demographic Characteristics

Parameter	Statistics	BioIron (N=30)
Age (years)	N	30
	Mean	33.7
	SD	10.59
	Median	32
	(Min, Max)	(18,55)
Weight (kg)	N	30
	Mean	64.09
	SD	14.63
	Median	65.90
	(Min, Max)	(35,88)
Height (cm)	N	30
	Mean	153.51
	SD	11.85
	Median	154.65
	(Min, Max)	(106,170)
Body Mass Index (kg/m^2)	N	30
	Mean	26.70
	SD	6.08
	Median	25.82
	(Min, Max)	(15,38)
Gender	Male	3(10%)
	Female	27(90%)
Tobacco History [n (%)]	User	0
	Non User	30(100%)
Drinking History [n (%)]	Drinker	0
	Non Drinker	30(100%)
Vegetarian /Non Vegetarian [n (%)]	Vegetarian	2(6.67%)
	Non Vegetarian	28(93.33%)

N= Total number of subjects in the group
n= number of subjects in the given category
SD= Standard Deviation
(Min, Max)= (Minimum, Maximum)

Analysis of mean change from Screening to Day 56 using non-parametric Wilcoxon signed rank test

Parameter (n=30)	Visit	Median (IQR)	Wilcoxon signed rank test P- value
Haemoglobin (g/dL)	Screening	11.95 (1.5)	0.0001
	Day 56	12.80 (1.5)	
	Mean Change from screening to Day 56	0.50 (3.25)	
Platelet Count (/cu mm)	Screening	287000 (72250)	0.0001
	Day 56	319000 (76750)	
	Mean Change from screening to Day 56	23500 (30500)	
Leukocyte count (cells/cu mm)	Screening	7800 (2150)	0.0001
	Day 56	9000 (1775)	
	Mean Change from screening to Day 56	750 (1175)	
Erythrocyte Sedimentation Rate(mm/hr)	Screening	22 (7)	0.001
	Day 56	18 (8)	
	Mean Change from screening to Day 56	-2.50 (4)	
Serum Iron (µg/dL)	Screening	59.00 (41.0)	0.178
	Day 56	53.00 (50.8)	
	Mean Change from screening to Day 56	5.0 (27.50)	
Total Iron Binding Capacity (µg/dL)	Screening	458.00 (96)	0.015
	Day 56	428.50 (75)	
	Mean Change from screening to Day 56	-9.5 (29.0)	
Serum Ferritin (ng/mL)	Screening	10.30 (37.64)	0.082
	Day 56	27.50 (38.18)	
	Mean Change from screening to Day 56	3.30 (31.37)	

Table 2: Analysis of mean change from Screening to Day 56 using non-parametric Wilcox on signed rank test

Parameter	Visit	n	Median (IQR)	Wilcox on signed rank test P- value
Haemoglobin (g/dL)	Mean Change from screening to Day 56	30	0.50 (3.25)	0.0001***
Platelet Count (/cu mm)	Mean Change from screening to Day 56		23500(30500)	0.0001***
Leukocyte count(cells/cu mm)	Mean Change from screening to Day 56		750(1175)	0.0001***
Erythrocyte Sedimentation Rate (mm/hr)	Mean Change from screening to Day 56		-2.50(4)	0.001**
Serum Iron (µg/dL)	Mean Change from screening to Day 56		5.0(27.50)	0.178
Total Iron Binding Capacity(µg/dL)	Mean Change from screening to Day 56		-9.5(29.0)	0.015*
Serum Ferritin (ng/mL)	Mean Change from screening to Day 56		3.30(31.37)	0.082
n = number of subjects in the given category *IQR= Inter quartile range*				

TABLE 3: Analysis of change from screening to visit 5 for SF-36 questionnaire and Fatigue severity scale

Parameter	Visit	n	Mean(SD)	Median(IQR)	Wilcox on signed rank test P value
SF-36 questionnaire	Change from Screening to Visit 5 (Day -56)	30	6.89(7.58)	2.56(8.99)	0.0001***
Fatigue severity scale	Change from Screening to Visit 5 (Day -56)	30	-1.07(0.65)	-1.00(0.40)	0.0001***
n : number of subjects in given characteristics *SD : Standard deviation* *IQR: Inter quartile range*					

FIGURES

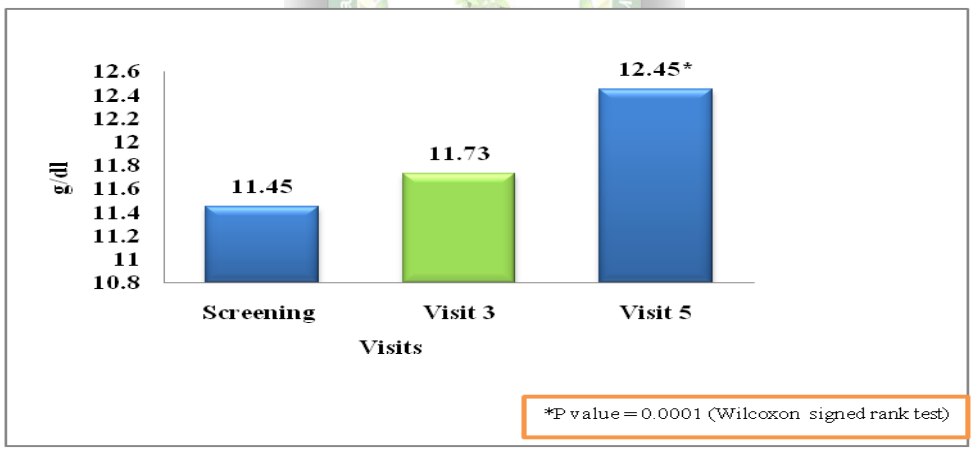

Figure 1: Mean change in Haemoglobin over the visits

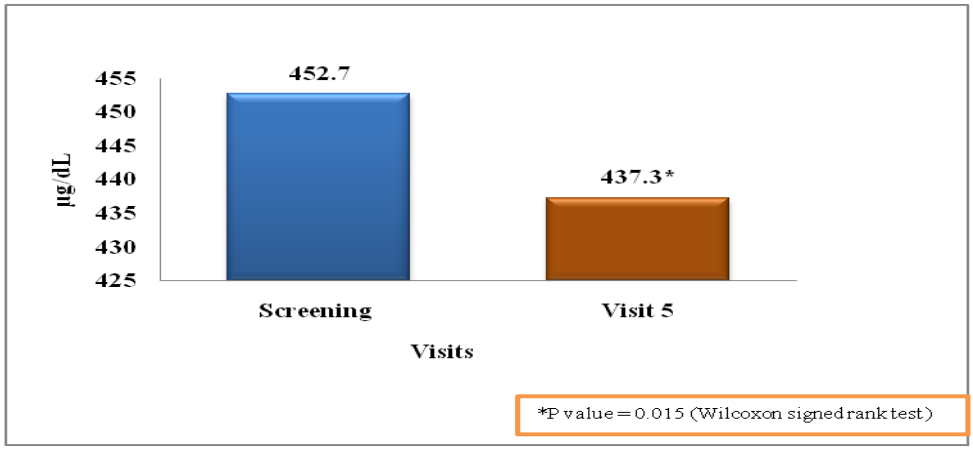

Figure 2 : Mean change in Total Iron Binding Capacity over the visits

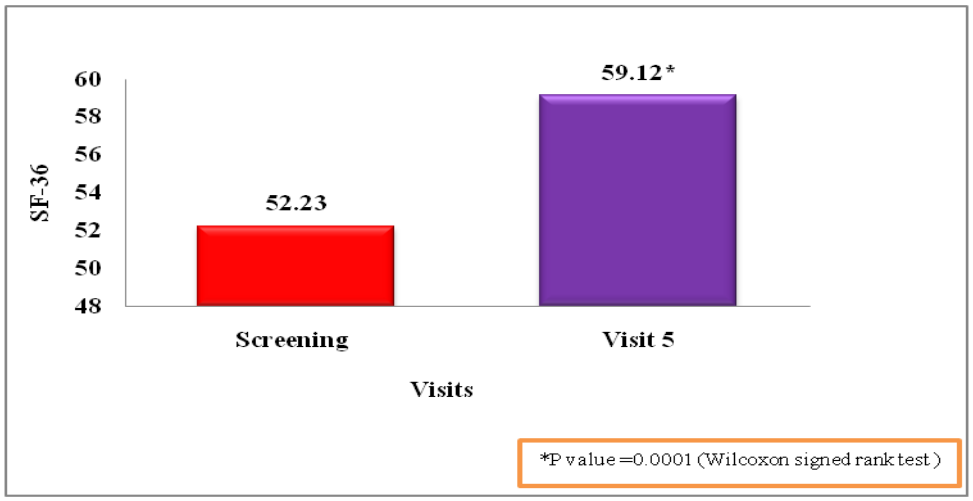

Figure 3: Mean change in SF-36 Health Questionnaire over the visits

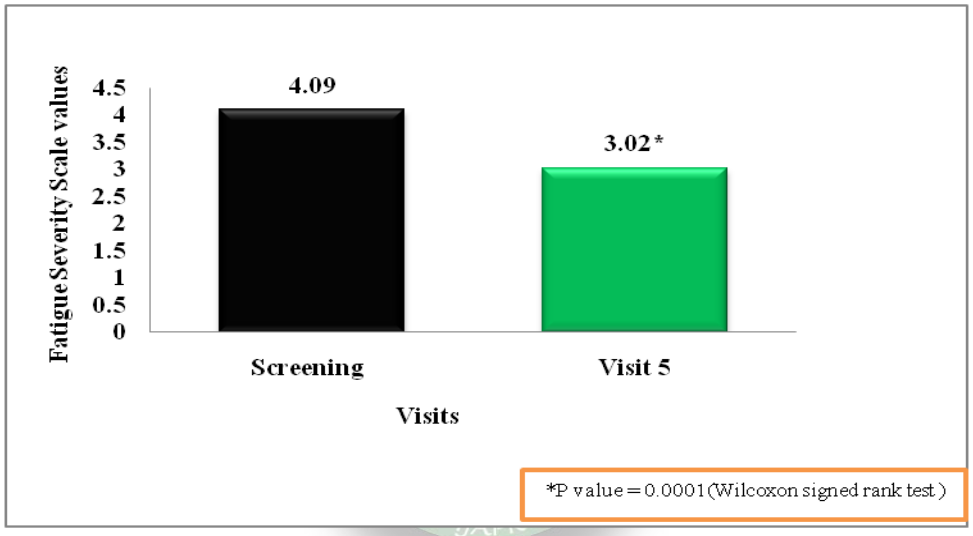

Figure 4: Mean change in Fatigue Severity Scale over the visits

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