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Evaluation of the Clinical Efficacy of Comparison of Irocibin Iron Polymaltose (Herbal Complex) and Iberet for the Treatment of Iron Deficiency Anemia

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ABSTRACT

A comparative clinical response was carried out on test complex herbal iron polymaltose (Irocbin Malt) vis a vis control ferrous sulfate (Iberet) for one month for safety and efficacy in 50 each for both arm patients for iron deficiency anemia (IDA). The mean corpuscular volume (CV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (CHC) levels were determined in patients. The statistical analysis of variance showed significant p value in test< 0.006 and control group sp < 0.048 of IDA in all hematological parameters. There was no adverse effect with the use of Irocbin Malt and this has found good acceptability by all treated IDA patients.

Keywords: Irocibin Iron Polymaltose, Ferrous Sulfate, Hemoglobin, Iron Deficiency Anemia.

INTRODUCTION

Iron deficiency is one of the most common disorders worldwide, affecting a large proportion of children and women in Pakistan. In addition, iron deficiency is the only nutrient deficiency of significant prevalence in all developing countries[1]. Pregnant women, growing children and elderly people with malaise causing blood loss are at risk with in the population[2]. Iron-deficiency anemia is characterized by the sign of pallor (reduced oxyhemoglobin in skin or mucous membranes), and the symptoms of fatigue, light headedness, and weakness. In a randomized trial, patients with anemia treated with intravenous (IV) iron carboxymaltose experienced improvements in symptoms, functional capacity and quality of life [3,4].

The hemoglobin concentration, which measures larger deficits in the functional iron compartment. The measurement of hemoglobin concentration and other red blood cell parameters is well standardized [5].Mean Corpuscular Volume is employed to differentiate between types of anemia on the basis of red cell size. Its Normal reference range 76 fl – 100 fl, If> 100 fl, then macrocytic anemia, If < 76 fl, then microcytic anemia and Calculated as Hematocrit / RBC count[6].Mean Cell Hemoglobin (MCH) is the average mass of hemoglobin per red blood cell in a sample of blood. Its Normal reference range is 27 – 31 pg / cell, the value decreases in hypochromic anemia's and increases in hyper chromic anemia's. Mean Cell Hemoglobin Concentration (MCHC) is a concentration of hemoglobin in a given volume of packed red blood cell Normal reference range is 32 – 36 g/dl. It is calculated as hemoglobin / hematocrit[7].

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METHODOLOGY

The study was based on an experimental clinical trial of test Irocibin Malt complex and control Ferrous sulfate (IBERET 500 liquid Abbott) were utilized for the treatment of iron

deficiency anemia. Clinical history, physical and biochemical examination of the registered patients at the base line were recorded and were monitored on each follow up. This was a case control, observational, multicenter evaluation based study, conducted on the patients living in the Gadap Town adjacent Madinat-al-Hikmah, Hamdard University, Karachi. They patients were registered either at Shifa-ul-Mulk Memorial Hospital, Karachi, Amna Unani Hospital, New Karachi, or Brooks HealthCare Centre Surjani Town, all hospitals are located in the Gadap Town, Karachi. The patients were registered and thereafter follow up was carried from November 2010 to November 2012. The study protocol, case record forms, regulatory clearance documents, product related information and informed consent forms were submitted to the Institutional Ethics Committee, and were approved by the same. Data were collected on clinical trial proforma and was analyzed on SPSS.

Diagnostic technique

Patients were examined clinically and the patients having the sign and symptoms of iron deficiency anemia were enrolled in the study. Clinical evaluation proforma was filled up before starting the treatment at baseline and the clinical record was continuously updated during the course of the treatment at every scheduled visit of the patient. The diagnosis of iron deficiency anemia was determined on the basis of blood Hemoglobin (Hb), Red blood cells count (RBC), packed cell volume (PCV),Man Corpuscular Volume (MCV), Mean corpuscular Hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC) as gold standard test for the diagnosis and base line confirmation of iron deficiency anemia. The test group consists of herbal formulations as syrup Irocibin Malt comprises of different herbal medicinal plants components and is delineated in dosage form design section. The control group is Ferrous sulfate syrup (IBERET 500 liquid Abbott).

Study procedures

The 50 patient search for both the group of iron deficiency anemia attending the out-patient department at Shifa-ul-Mulk Memorial Hospital Karachi, Amna Unani Hospital, New Karachi, and Brooks Health Care Centre, Surjani Town were included in the study and were divided arbitrarily randomized into Test Drugs Irocibin Malt were prescribed to test groups and Syrup Ferrous sulfate (Iberet liquid (Abbott) were administered to control groups for 04 weeks in a random manner. Detailed history and clinical examination was done as per the proforma designed for this study. Adverse effects if any were recorded by the physician monitoring the patients enrolled for the study.

All the patients were followed up weekly and monitored for general physical examination and improvement in sign and symptoms was recorded on every scheduled visit. Beside that Hemoglobin level and Complete blood count (CBC) was recorded at the end of every 4 week after one month of treatment. The study period include was from November 2010 to November 2012.

Inclusion and Exclusion Criteria

Inclusion Criteria: The patients only suffering from Iron deficiency anemia and living in Gadap Town Karachi. Patients having no obvious pathological finding on routine examination. All socioeconomic classes including lower middle and higher. Male and female patients between 05 to 60 years of age. Exclusion Criteria: The patients belonging to the distant area outside Karachi were excluded because of inherent difficulty in follow up. Also patients suffering from unstable angina. uncompensated congestive cardiac failure, poorly controlled arrhythmia; uncontrolled hypertension [>150/95 mm Hg]Dialysis., history of organ

Table 1. Description of the Ingredients ofIrocibin Malt

S.No	Ingredients	Tag Number	Quantity (mg/5ml)	Quantity (KG/Batch)
1	*Rosadamascene* Mill. *(Gul-e-Surkh)*	IROM-R15	50mg	450 grams
2	*Zizyphus jujuba* Mill. *(Unnab)*	IROM-Z16	50mg	275 grams
3	*Eletteria cardamomum* Maton.*(Ilaichi)*	IROM-E17	50mg	52 grams
4	*Prunus armenica* Linn. *(Khobani)*	IROM-P18	50mg	1670 grams
5	*Prunus domestica* Linn. *(Aloo Bukhara)*	IROM-S19	50mg	275 grams
6	*Punica granatum* Linn. *(Anar dana)*	IROM-P20	75mg	275 grams
7	*Phyllanthus emblica* Linn. *(Amla)*	IROM-P21	50mg	275 grams
8	Iron Polymaltose complex (elemental iron BP)	IROM-I22	25mg/5ml	500 gm

transplantation, hemochromatosis and haemosiderosis.

Dosage Form Design:

Irocibin Malt Complex: The syrup IRO-C-BIN malt was prepared from different herbal ingredients which were purchased from Insaf Karyana Store Jodia Bazaar, Karachi, in the month of November 2010. The ingredients utilized *Rosa damascena* Mill. *(Gul-e-Surkh)* 50mg/5ml, *Zizyphus jujuba* Mill. *(Unab)* 50mg/5ml, *Elettaria cardamomum*(L.) Maton. *(Ilaichi) 50mg/5ml, Prunus armenica Linn. (Khoba*ni)50mg/5ml, *Prunus domestica* Linn. (*Aloo Bukhara)* 50mg/5ml, *Punica granatum* Linn. (*Anar dana)* 75mg/5ml, *Phyllanthus emblica* Linn. *(Amla)* 50mg/5ml, are the same as that of Irocibin but to it iron polymaltose was added. After the syrup was prepared, as given earlier for Irocibin, the Iron polymaltose 500 gm. was added directly into the prepared Irocibin by gently adding and stirring the syrup for the solubilization of iron polymaltose in the syrup completely. The value calculated of Iron polymaltose is as follows. Every 5ml of Irocibin complex was added 100 mg of Iron(III) Hydroxide polymaltose Complex INN, equivalent to elemental iron 25mg, so 120 ml of Irocibin MALT contain 2400mg of Iron polymaltose so it shows that every 5ml of Irocibin MALT contain 25mg of elemental Iron. *Composition:* Irocibin MALT Liquid: Each 5ml contains:

Indications: Iron deficiency anemia. Prophylaxis and treatment of iron deficiency anemia. Promotes hematopoiesis, lack of appetite & growth Dosage forms: Syrup. Pharmacotherapeutic group: Haematinic.

Pack Size: 120ml bottle. Excipients: sugar, sodium benzoate, orange flavour. Contra indications: Hemochromatosis, Haemolytic anaemia, Haemosiderosis. Hypersensitivity to any of the ingredients. Dose: Adults and the elderly its dose is For Treatment: 2-3 tea spoon a

day in divided doses. For Prevention: 2 tea spoon a day. Children having age between 6-12 years its dose in treatment is Children weighing over 22kg: one tea spoon a day. Children weighing over 44kg: one tea spoon twice a day. Children weighing over 66kg: one teaspoon three times a day. Side effects: Abdominal discomfort only in few patients

Ferrous Sulfate (IBERET-500 Syrup)

Iberet-500 syrup is a proprietary product of Abbott Laboratories (Pakistan) Ltd., Landhi, Pakistan which is used for the prevention and treatment of iron deficiency anemia, especially with associated nutritional deficiencies. It belongs to the group of medicines termed as iron supplements. Iron is necessary for the production of blood cells. When body is unable to produce required number of blood cells due to deficiency of iron it leads towards a medical condition named as iron deficiency anemia. **Ingredient(s):** Iberet-500 Liquid: Each teaspoonful (5ml.) contains.

Table 2. Description of the ingredients of Ferrous Sulfate (IBERET-500 Syrup)

S.No	Ingredients	Quantity
1	Ferrous sulphate U.S.P	131 mg (represents 26.25mg of elemental iron),
2	Vitamin B12 U.S.P	6.25mcg
3	Vitamin C U.S.P./ Eur.P.	125mg
4	Vitamin B1 U.S.P	5mg
5	Vitamin B2 U.S.P	1.5mg
6	Vitamin B6 U.S.P	1.25mg
7	Nicotinamide U.S.P.	7.5mg
8	Dexpanthenol U.S.P.	2.5mg.

Indications: Iron deficiency anaemia. Prophylaxis and treatment of iron deficiency anemia. Promotes haematopoiesis, lack of appetite & growth. **Dosage forms:** Syrup. **Pharmacotherapeutic group:** Haematinic. **Pack Size:** 120ml bottle. **Pharmacokinetics:** Its oral absorption is only 20%. **Contra indications:** Hemochromatosis, Haemolytic anaemia, Haemosiderosis. Hypersensitivity to any of the ingredients. Dose: Adults and the elderly its dose is For Treatment: 2-3 tea spoon a day in divided doses. For Prevention: 2 tea spoon a day. Children having age between 6-12 years its dose in treatment is Children weighing over 22kg: one tea spoon a day. Children weighing over 44kg: one tea spoon twice a day. Children weighing over 66kg: one teaspoon three times a day. **Side effects:** Side effects are less frequent but sometime they are not tolerable. Common side effects are mentioned as under: Nausea, Epigastric discomfort, Diarrhoea, Black stool, Constipation, Staining of teeth.

Tests and duration of the treatment: Total duration of treatment of 4 weeks (one month), thereafter with a window of 15 days. Hematological parameters were Hemoglobin level (HB %). Mean corpuscular volume (MCV). Mean corpuscular Hematological Hemoglobin concentration (MCHC). Serum ferritin level. Measurement before start of treatment at the baseline. Measurement at the end of treatment at the end one month (4 weeks). Normal values of RBC: Total RBC Normal count: Male: 4-5 million/cmm; Female: 3.5- 4.5 million/cmm. Hemoglobin Normal: Male: 12-16 Gms%; Female: 37-47Gms%. Hematocrit (Packed Cell Volume) (PCV) Normal: Male: 40-50%; Female: 37-47%.

RESULTS AND DISCUSSION

Iron deficiency anemia occurs when the body does not store enough iron or cannot absorb enough iron to help build red blood cells. The anemia means that red blood cells is abnormally low, thus causing it does not carry enough oxygen to all parts of the body. In order to cure

the iron deficiency there are two choices, first the iron supplements that is administration or prescribing ferrous sulfate syrup but the ferrous sulfate can exert some serious or less serious side effects as narrated. The iron over dose symptoms may include nausea, fever, stomach pain, bloody diarrhea, blood in coughing or vomit, shallow breathing, weak and rapid pulse, pale skin, blue skin and seizure. Ferrous sulfate side effects may include constipation, upset stomach, black or dark colored stool, temporary staining of the teeth. Therefore the second option is the use of medicinal herbs containing appreciable quantities of iron in calculated and formulated form to treat iron deficiency anemia. Beside using such natural supplements to wipe out iron deficiency anemia, the advantages could be obtained with additional nutritional supplements as an extra benefit to overcome vitamin deficiency in the body which is very much associated with iron deficiency but how does the herbs have the advantage to provide sufficient quantity of iron to the body so that hemoglobin increase to standard level of 12 gm/ dl.

The test drug Irocibin Malt and control drug Iberet syrup are treated in the statistical parameters as follows.T he most common clinical features associated with anemia are breathlessness, tachycardia, poor appetite, easy fatigue, headache, irritability dizziness and general weakness etc. All the clinical features were noted before and after treatment and comparative analysis was done at the end of treatment. The comparisons of the two groups were done by using Anova and statistically significant improvement was noted in all groups after treatment. It is concluded that all the drugs have significant importance to reduce

Table 3. Overall improvement in intensity of symptoms by Test drug Irocibin Malt complex analyzed by Wilcoxon Signed Rank Test

Intensity of symptoms					
Symptoms	Baseline (T0)		After treatment (T1)		
	Median	IQR	Median	IQR	p value
Breathlessness	3	1-4	1	1-2	0.01
Tachycardia	4	1-4	1.5	0-1	0.002
Poor Appetite	3	1-4	1	1-2	0.01
Headache/ Dizziness	4	1-4	2	1-3	0.03
Fatigue/Weakness	3	1-4	1	0-1	0.02

Table 4. Overall improvement in intensity of symptoms by Control drug Iberet analyzed by Wilcoxon Signed Rank Test

Intensity of symptoms					
Symptoms	Baseline (T0)		After treatment (T1)		
	Median	IQR	Median	IQR	p value
Breathlessness	3	1-4	1.5	1-2	0.05
Tachycardia	3.5	1-4	2	0-1	0.02
Poor Appetite	3	1-4	1	1-2	0.01
Headache/ Dizziness	4	1-4	2	1-3	0.03
Fatigue/Weakness	3	1-4	1.5	0-1	0.03

the clinical symptoms related to anemia.

Therefore it can be deduced from the p values afforded for sign and symptoms, the test drug Irocibin Malt and control drugs Iberet syrup improves the sign and symptoms well, which may be due to the nutritional component in case of test drug along with iron contents while the control drugs Iberet only iron component improves the sign and symptoms but associated with side adverse effects.

Improvement in intensity of clinical features calculated by Wilcoxon signed Rank Test: Intensity of symptoms is the parameter to record the level of improvement. In this study, intensity of symptoms was recorded as absent: 1, mild: 2, moderate: 3 and sever: 4 at baseline (T0) and after the completion of treatment (T1). Median values, interquartile ranges (IQR) were determined and p values were calculated by using Wilcoxon signed-rank test to record the indirect effects of multiple groups in the improvement of Hb level and clinical features associated with anemia.

Improvement in intensity of clinical features by Test drug: Test drug Irocbin Malt showed marked symptomatic improvement in all anemias related clinical features after treatment as shown in table 3, fig. 01.

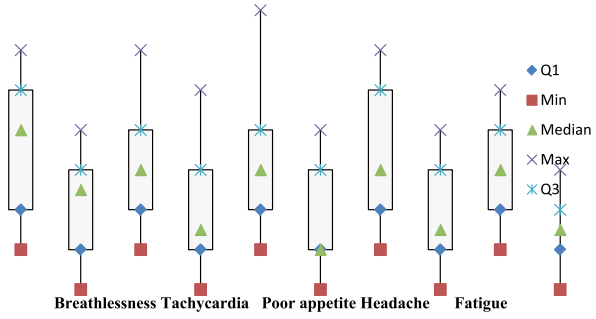

Fig. 1. Improvement in symptoms by Irocbin Malt (Test drug)

Improvement in intensity of clinical features by Control drug Iberet was measured by Wilcoxon and showed in Table 4 and fig. 02.

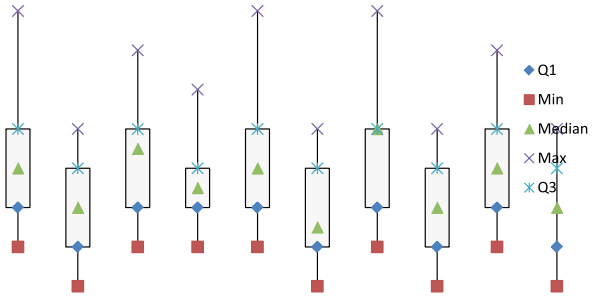

Fig. 2. Improvement in symptoms by Iberet (Control drug)

Object of this study was to compare herbal coded formulation comprising of different medicinal plants with control drugs available in the market to see whether these may represent a platform for the development of novel therapeutics. It was observed that there is a marked improvement in hemoglobin level of patients treated with Test drug "Irocbin Malt . It may be hypothesized that this improvement in the Hb level might be due to the presence of Maltose in the coded formulation which exerts beneficial effects as discussed in the literature. Furthermore, there was significant improvement in overall subjective signs and symptoms in all treated groups.

Iron deficiency anemia treatment in a comparative manner with ferrous sulfate and iron polymaltose complex was done by Bopche *et al* and reported that the clinical response and side effects of Ferrous sulfate is better and less significant adverse effects during the iron deficiency anemia in children [8]. Patil *et al.* have reviewed that oral iron therapy is the commonest treatment and large number of iron salts is available in market for oral iron therapy. In clinical practice oral iron supplementation commonly used are Fe sulfates, Fe fumarate. These conventional iron preparations have more gastrointestinal intolerance. There are many new iron salts marketed (Fe bisglycinate, Carbonyl iron, Iron polymaltose complex etc.) which claim to have low gastrointestinal intolerance, increase Hb level faster and

improve iron stores better than conventionally used iron salts. Thus conventional iron preparations still can be considered as best cost effective choice with tolerable side effects for prophylaxis and treatment of iron deficiency anaemia [9].Kambar and associates compared efficacy, safety, compliance and cost-effectiveness of ferrous sulfate (FS) with IPC in antenatal women. 100 antenatal women with 14 to 20 weeks of gestation were recruited in the study, one group of 50 women was given FS and the other group of 50 women was given IPC for 6 weeks. Hemoglobin concentration (Hb), packed cell volume (PCV), Mean Corpuscular Hemoglobin concentration and serum iron were estimated before and after treatment with the above iron formulations. Compliance with pill count and safety with adverse effects monitoring in follow-up were noted. Statistical analysis was done with student's T test and chi square test. The improvement of hematological parameters was comparable in both groups statistically but compliance and safety were better with the IPC group when compared to FS group. IPC is a better alternative to FS as it is safe and showed more compliance[10].

All the patients enrolled in the study were evaluable for safety. Side effects were defined as sign and symptoms that first occurred or became more severe during the course of treatment. The majority of adverse events were assessed as mild in severity and self-limiting in nature. Therefore, none of the patients withdrew from the study due to these adverse events. Adverse events categorized by the clinical investigator as possibly or definitely drug related in patients administered No life threatening side effects recorded in any group. It is because of the fact that plant drug selected for the treatment of anemia does not contain any chemical agent that may trigger the adverse drug reaction response. This can be explained further that chemical components of the plant drugs altogether are low in the frequency of occurrence and even administered together in synergistic fashion exhibit pronounced type of effective response for curative action.

CONCLUSION

The objective of this research was to characterize iron deficiency with the use of herbal-Polymaltose and allopathic and elements. The test and control drugs were administered to two groups of patients registered on the bases of inclusion and exclusion criterion parameters. Thereafter preliminary screening of Hb analysis, these drugs were prescribed and administered for 30 days and further windows of 30 days so as to assess the compliance of effectiveness of the mode of treatment. Over all the Irocibin Malt as test drug was found to be superior over Iberet. The combined results indicate that consequently the choice of drug based on herbal components along with iron elements such as in the case of Irocibin Malt is the best choice where the iron deficiency anemia along with nutritional deficiency anemia could be controlled from efficacy point of view. The finding from this study demonstrated the following salient clinical assessment; there was statistically significant difference when comparing the effectiveness of test drug "Irocibin Maltcomplex" to other experimental and test groups for the improvement of hemoglobin level in the blood as well as improvement in subjective clinical features. This is also the first demonstration and characterization of using herb-mineral drug and its important clinical implications on the strength of the evidence that iron deficiency or anemia. Study has been focused on comparing ferrous sulfate preparations with ferric iron polymaltose herbal ingredient complex preparations, the two predominant forms of iron used which has given their good bioavailability, efficacy, and acceptable tolerability demonstrated. The results of the present study suggest that iron poly maltose if

mixed with herbal ingredients to address iron deficiency anemia can be considered as a useful alternative formulation for the treatment.

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