An integrated approach to iron deficiency anemia

Halima Nazar* & Khan Usmanghani
Faculty of Eastern Medicine, Hamdard University, Karachi, Pakistan
E-mail: haddiii@yahoo.com

Received 21 August 2014, revised 19 September 2014

Iron deficiency is a common nutritional disorder in developing countries and contributes significantly to reduced work productivity and economic output as well as to increased morbidity and mortality. There are well established biochemical tests for assessing iron status in developed countries. However, cost and interference from infectious conditions make it difficult to assess iron status in many developing country settings. Examination of the hemoglobin distribution in the population and assessment of the hemoglobin response to supplementation are alternative approaches to defining iron status and the nature of anemia. Prevention and control of iron deficiency requires the combined approach of dietary improvement, fortification of a common staple food when feasible, and appropriate iron supplementation for infants and pregnant women. In all these intervention activities, operational research is needed to improve effectiveness. In addition, controlling iron deficiency requires coordination with other nutrition and primary healthcare programs as part of an integrated approach to improved health and nutrition of the population. A randomized, controlled double blind clinical trial was conducted to compare the efficacy and safety of herbal medicinal treatment syrup Sharbat-a-Folad versus syrup Ferplex for the treatment of Iron Deficiency Anemia.

Keywords: Iron deficiency, Herbal medicine, Anemia

IPC Int. Cl.: A61K 36/00, A01D 20/32, A01D 20/00

Iron deficiency anemia (IDA) is the most common nutritional deficiency worldwide. It can cause reduced work capacity in adults\(^1\) and impact motor and mental development in children and adolescents\(^2\). There is some evidence that iron deficiency without anemia affects cognition in adolescent girls\(^3\) and causes fatigue in adult women\(^4\). IDA may affect visual and auditory functioning and is weakly associated with poor cognitive development in children.

The term "anemia" is used for a group of conditions in which the number of red blood cells in the blood is lower than normal, or the red blood cells don’t have enough haemoglobin. The estimates of the prevalence of anemia vary widely and accurate data are often lacking, it can be assumed that significant proportions of young children and women of childbearing age are anemic\(^5,6\).

Iron deficiency results when iron demand by the body is not met by iron absorption from the diet. Thus, patients with IDA presenting in primary care may have inadequate dietary intake, hampered absorption, or physiologic losses in a woman of reproductive age. It also could be a sign of blood loss, known or occult. IDA is never an end diagnosis; the work-up is not complete until the reason for IDA is known.

The risk factors associated with iron deficiency anemia includes: low socioeconomic status, race as black women have a lower mean hemoglobin and a wider standard deviation than white women, inadequate dietary intake or parity, suggesting there may be an unidentified, possibly racial factor predisposing these women to iron deficiency\(^7\).

Anemia cannot be reliably diagnosed by clinical presentation. Fatigue, the most common reason to check hemoglobin, was caused by anemia in only one out of 52 patients in a primary care practice\(^8\). In a hospital setting, pallor predicted anemia with a likelihood ratio (LR) of 4.5. However, absence of pallor was less helpful at ruling out anemia, giving an LR of 0.6 even when anemia was defined as less than 9 gm per dL (90 gm / L), a lower diagnostic level than that of the WHO or CDC\(^9\). Other classic symptoms such as koilonychia (spoon nails), glossitis, or dysphagia are not common in the developed world\(^10\).

*Correspondence author
The diagnosis of IDA requires that a patient be anemic and show laboratory evidence of iron deficiency. Red blood cells in IDA are usually described as being microcytic (i.e. mean corpuscular volume less than 80 µm$^3$ [80 fL]) and hypochromic, however the manifestation of iron deficiency occurs in several stages. Patients with a serum ferritin concentration less than 25 ng / mL (25 mcg / L) have a very high probability of being iron deficient. The most accurate initial diagnostic test for IDA is the serum ferritin measurement. Serum ferritin values greater than 100 ng per mL (100 mcg / L) indicate adequate iron stores and a low likelihood of IDA.

In some populations, such as those with inflammatory disease or cirrhosis, these tests must be interpreted slightly differently because ferritin is an acute-phase reactant. Cutoffs for abnormality in these patients generally are higher.

Another laboratory change that occurs in patients with IDA is an increase in the iron-carrying protein transferrin. The amount of iron available to bind to this molecule is reduced, causing a decrease in the transferrin saturation and an increase in the total iron-binding capacity. The serum transferrin receptor assay is a newer approach to measuring iron status at the cellular level. Increased levels are found in patients with IDA, and normal levels are found in patients with anemia of chronic disease.

The treatment arms were chosen by block randomization in batches of eight using computer-generated random numbers is being used to assign women to one of the four combinations of trial intervention. Block randomization was chosen to ensure that the experimental groups would not become unbalanced if the rate of recruitment at sites differed greatly. A research fellow with no other role in the project is overseeing the labeling and packing of all the trial medications and holding the randomization schedule until the code is broken.

**Level of significance**

This is the set standard to decide the cut-off value between treatment groups when comparing the two groups. If the results are significant at this set level ($\alpha = 0.05$) the null hypothesis will be rejected.

**Patients, materials and methods**

**Study design**

The study was based on an experimental, randomized double blind clinical trial. The study had been conducted according to principles of good clinical practice (i.e. an informed consent was obtained before enrollment and proper history and clinical examination were recorded on each follow up), and the study was carried out during May 2003 to June 2004. A randomized double blind experimental design was employed to test the hypotheses; therefore, by manipulating the independent variable (Efficacy, side-effects) any effects on the dependant variable (herbal and allopathic treatment) could be monitored.

**Patients**

The study was conducted on 50 patients aged 12-40 yrs (Fig. 1) who were attending gynecological out patient visits in Shifa-ul-Mulk Memorial Hospital.

**Setting**

The study was conducted in the Department of Gynecology and Obstetrics at Shifa-ul-Mulk Memorial Hospital for Eastern Medicine at Hamdard University in Karachi.

**Sample selection**

In this study only the patients selectively enrolled, were diagnosed with iron deficiency anemia through clinical history and laboratory investigations were enrolled. Diagnosis of iron deficiency anemia was based on the typical signs and symptoms and laboratory finding. Complete blood picture (CBC), Hemoglobin, ESR, and urine (routine and microscopic) tests were also performed.

Recruiting GPs identify eligible women in their clinical practice and invite them to consider participation in the trial, after provision of sufficient information to make an informed decision. Women...
who meet the eligibility criteria and agree to participate are required to give written informed consent. Recruiting GPs also obtain demographic and relevant past and current medical data, particularly data relevant to risk factors for developing iron deficiency anemia. The interventions being tested are:

(i) Control group received allopathic treatment (Syrup Ferplex 2 teaspoon for 7 days), (ii) and the test group received the herbal medicine (syrup foulad 2 teaspoon for 7 days) All participants were observed for 3 follow-up visits over the course of treatment until they improved.

Blood samples were collected for CBC when the clinical picture shows the complete improvement to access the efficacy of the trial and confirmation and improvement in haemoglobin status. Same parameters were followed in control group.

Trialed medicine constituents
Control medicine Ferplex: Iron Hydroxide Poly Maltose Complex:50 mg/5ml
Test medicine syrup foulad: Vitis vinifera L. (Maveez munaqa), Phyllanthus emblica L. (Amla), Rosa damascena Herrm.(Gulab), Cichorium intybus L. (Kasni), Spinacia oleracea L.(Spinach), Amaranthus (Cholie, a variety of sag) and Ferrous sulphate in sucrose base Sweetening agents & preservative 0.0767 mg.

Assessment
The Normal haemoglobin count in reference to age set standard of WHO), blood morphology, was used as the primary outcome of the study. Secondary outcomes included the total symptoms score, the global assessment of the treatment by the investigator and the women safety of the drugs and severity of adverse events at each follow-up visit. The relationship of each event to the study drug was also assessed. The safety outcome measure was the incidence of treatment-emergent adverse events in both groups. A blood specimen for routine CBC was obtained prior to the treatment.

Inclusion criteria
Persons may be included in the trial if they meet the following criteria

- Patients suffering from Iron deficiency anemia's.
- Patients have proper screening of Iron deficiency via complete CBC and peripheral blood smear (Known cases)
- Patients living in Karachi, Pakistan.

Exclusion criteria
Patients were excluded if they have any of the following criteria

- Patients having other associated pathologies like uncontrolled diabetes, hypertension and liver disorders, etc.
- Patients having other types of anemia's like Protein deficiency Anemia, Pernicious Anemia, Sickle Cell Anemia. and Thalassaemia, etc.
- Known cases of failure iron therapy.
- Patients suffering from iron deficiency in secondary to Malignancies.
- Patient belonging to any area outside Karachi because of intrinsic difficulty to follow up.

Results
The present study is to investigate formulated herbal medicine syrup Foulad for the treatment of iron deficiency anemia. The clinical screening of haemopoietic activity between Foulad and Ferplex was carried out to determine the efficacy and side effects towards off this malaise. These evaluations were based on clinical and laboratory findings so as to ascertain the rate of improvement in haemoglobin. In this study the total of 50 patients were initially randomized and screened, the intent-to-treat population enrolled. The patients were evenly distributed to test or control group with the ratio of 1:1, i.e. 25 in each group. This loss was distributed evenly between the treatment groups. The demographic and baseline characteristics of the intent-to-treat group were comparable for the herbal medicine and allopathic medicine treatment.

Patient characteristics
There were no significant differences in the mean age (26.12 ± 7.92 vs. 26.48 ± 4.75 test and control group respectively (Table 1) values between the treatment groups at the start of the clinical trial. All the patients were distributed in 5-class interval ranging from age 12 to 40 yrs. The mean age of the married women’s were 32.0 vs. 32.46 and mean age of the single patients were 19.75 vs. 20.0.
Treatment assignment and follow-up

All subjects were clinically studied and completed assigned therapy during the period May 2001 to June 2004. Results presented below represent an intention-to-treat analysis, as stipulated by this study protocol. Baseline patient characteristics for all study variables were balanced among treatment groups (Table 2).

Baseline demographic variables

The baseline pre-treatment analyses of Iron deficiency anemia history and examination were performed. The clinical evaluation proforma of Iron deficiency anemia was filled at the time of enrollment in both treatment groups. Patient’s baseline demographic variables for Iron deficiency anemia history and general physical examination were summarized for each treatment group. As depicted in Table 2, patient characteristics were equally balanced between the test and control groups. The two treatment groups did not differ significantly (all p<0.05) from each other at any time point. The most common Iron deficiency anemia symptom was pallor 44.0 % in allopathic treated and 36.0 % in herbal treated patients. Whereas the common cause of iron deficiency anemia noted in this trial was the blood loss 56 % in allopathic treated and 52 % in herbal treated patients.

Baseline severity of anemia

The assessment of severity of iron deficiency anemia at the time of enrollment exhibited following results test group verses control group, mild anemia 7 patients (28%) vs. 10 (40%), moderate anemia 15 patients (60%) vs. 12 (48%), severe or anemia 3 patients (12%) vs. 3 (12%) patients noticed in the both treatment group. Baseline severity of anemia did not differ between the two groups. The baseline data comparative analysis by chi-square test confirms that there were no baseline differences among the treatment group as evident from p values in Table 2. The severity of anemia classified as per following international standards of haemoglobin: Mild 10-10.9 gm/dl, moderate, 7-10 gm/dl, severe < 7 gm/dl and very severe < 4 gm/dl.

Effects of therapy on hemoglobin status

Hemoglobin increased dramatically in both treatment groups after therapy (Fig. 2). The rates of the improvement in hemoglobin concentration were higher in the herbal treatment group at all times after treatment and it revealed that the efficacy of herbal treatment is as superior to allopathic treatment (P=0.001). The total duration of treatment was four weeks in both treatment groups. The clinical success rates on the basis of self-assessment of patient regression of complaints and physician examination on follow-up was more effective in test group (Fig. 2). Clinical failures or no significant improvement in hemoglobin after treatment occurred in 1/25 patients (4%) receiving herbal medicine and in 7/25 patients (28%) receiving allopathic medicines (Fig. 2). Clinical success rates for those with mild to moderate infections and those with severe infections were higher in test treatment group. For the overall, clinical success was observed in 15/25 patients (60%) of cases in herbal-treated patients and in 2/25 (8%) of cases in allopathic-treated patients.
Fig. 2—Improvement after treatment

The overall evaluation was mainly based on the efficacy of drugs in reducing anemia in terms of both objective and subjective symptoms. The syrup Foulad produced a better result than allopathic medicines, which showed an overall cure rate of 60% versus 8% significantly effective as confirmed by chi-square test the test treatment has superior efficacy than control treatment (p=0.001).

Safety evaluations
All the patients enrolled in the study were evaluated for safety. Adverse effects observed after administration of medicine are summarized in Table 3. The majority of adverse events were assessed as mild in severity. Adverse events categorized by the Physician (researcher) as possibly or definitely drug related were reported in 3/25 patients (12%) receiving herbal medicine and in 15/25 patients (60%) given allopathic medicine.

Nausea was the most common drug-related events among allopathic medicine (36 %) and herbal group (4%) recipients. Overall side effects (P = 0.010) were greater in control treated participants than in test participants. No severe or serious adverse side effects were observed that interfere with activities of daily living. Comparison of data recorded by participants relating to these variables showed highly significant differences between test and control groups for measurements side effects as shown in Table 3. Consequently the generated data rejected the null hypothesis (when P<0.05) hence the null hypothesis was rejected on the basis of statistical findings in regard to efficacy and safety.

Discussion
Iron deficiency anemia is most often a polysymptomatic disease. The use of allopathic drug combination has been considered as one of the effective therapy. But this is not feasible, as besides being cost prohibitive, they are not without side effects. The herbal formulation syrup Foulad contains herbs, which are known for its wide range of clinical use in indigenous medicine. It has been proved that these herbs exert profound activity for the improvement of hemoglobin percentage.

This uni-center trial demonstrated that herbal medicine was more effective in the management of patients with iron deficiency anemia. Among herbal treatment resulted in a 60% clinical cure or improvement rate, which is superior to that achieved with allopathic therapy 8% clinical success rate. The response rate of hemoglobin improvement status before and after treatment suggests that syrup Foulad has the higher efficacy as allopathic medicine (p>0.001).

In the light of study that I have presented, it is concluded that phytomedicine administered under a randomized double blind trial are exhibiting desirable effects with profound margin of safety. The plus point is that the formulations is absolutely cost effective and has shown promising results even in survive lance studies. The spectrum of herbal medicine has been widening following the modalities of integrated medicine like our eastern system of medicine.

The medicinal word is switching over to alternative medicine including herbal medicine especially South Asia due to its tremendous potential that is being confirmed by current researches. In this uni-center study, Syrup Foulad was well tolerated and had a rate of drug related adverse events less than to that of patients treated with Syrup Ferplex (p = 0.010). Mild nausea was the most commonly reported adverse events in test treatment groups and control group.

Conclusion
Based on the statistical result of present clinical trial it can be concluded that:

<table>
<thead>
<tr>
<th>Table 3—Side effects on patients self assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed Side-effects</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>No Complaints</td>
</tr>
<tr>
<td>Total Patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No Complaints</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>
• A comparative evaluation of the Iron deficiency anemia treatment by *Sharbat Foulad* vis a vis the *Syrup Ferplex* differ in treatment response, the herbal medicine is superior to allopathic medication.

• There was less untoward manifestation associated with the use of syrup *Foulad* and this is found a good acceptability by most of the treated patients. *Syrup Foulad* has added benefit of safety.

References


