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Effect of Mixture of Figs, Dates and Currants on Symptomatology and Changes in Haematology and Biochemical Markers of Iron Deficiency Anaemia

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Abstract

Background: Iron deficiency is a major cause amongst those of anaemias arising due to inadequate nutrition, worldwide. A large number of iron deficiency cases can be prevented with timely, adequate and appropriate intervention. Anaemia is a major health issue in the developing nations including India with over nearly 70% children affected by it. Around 73 million children suffer from varying degrees of anaemia before they attain the age of three. Pāṇḍu, is a disease narated in Āyurveda, is supposed to be the closest ailment entity similar to that of anaemia, symptomatically. IDA can be effectively managed by providing adequate iron substrate or biological iron through diet. Chemical iron preparations present with various unwarranted effects viz. constipation, vomiting, metallic taste, causing deposits of iron in the tissues which might lead to iron toxicity. Iron from biological origin (from plant and animal origin), also known as biological iron or bio-iron can reduce these symptoms and unwarranted effects to a greater extent, it can be readily absorbed by the human body and readily bio-converted into haemoglobin.

Methodology: This interventional study had supplemented iron from dietary origin i.e biological form of iron from dietary sources using a folklore combination of Figs, Black Currants and Dates fruit, which are considered to be a rich source of iron of biological origin, for the management of children suffering from iron deficiency anaemia of mild to moderate grade.

Results and Conclusions: The trial combination was studied on symptomatology and measured on hematological and biochemical markers of iron deficiency anaemia and it was found to have positive effect with reduction in symptoms, on increasing haemoglobin levels, iron level and ferritin levels in the serum and a marked fall in total iron binding capacity.

1. Introduction

Anaemia is a significant health issue having an impact on human productivity in general, growth and development of children and health in general of the majority of the population in India and particularly in the developing countries. As per the published data, specifically for anaemia, by the National Family Health Survey of the Government of India, its prevalence among children under the age of three years of, showed about five per cent increment than the previous survey conducted by the same agency, a few years ago. About 73 million children below the preschool age (79%) suffer from varying degrees and severity of anaemia. In the Indian population, over 50 million children suffer from moderate-to-severe anaemia, arising of varying origins. According to NFHS study, the highest prevalence is among the age group of late infancy to below two years. Based on studies by the National Nutrition Monitoring Bureau, iron deficiency anaemia prevalence among children between one to five years of age is around 2/3rd of the

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total age group population, across different states of India. Anaemia in childhood can cause an irreversible damage, physically and intellectually in particular in relation to the growth and development of a young child. The numbers are disheartening. Nearly more than two billion people – over 1/3rd of the world's population – are anaemic, with varying severity, mainly due to iron deficiency along with deficiency of other nutrients known to be responsible to prevent IDA.

One can understand IDA as a syndrome of blood disorder in where the capacity of carrying oxygen by the blood or one can say as the ability to carry oxygen by the blood is reduced. This is due to a reduced number of red blood cells in the circulating blood, or a reduction in the amount of hemoglobin in the RBC. "Anaemia" is not a complete diagnosis in itself, but is a sign indicating the presence of other underlying pathologies which have culminated in developing anaemia. Iron deficiency due to any cause, inadequate intake or excessive loss, is mostly considered to be the most common cause of nutritional type of anaemia, in children and females, though other components of nutrition such as vitamin B_{12} (cyanocobalamine) and folate (folic acid) deficiencies, intestinal parasitic infections, blood parasites like plasmodium and leishmenia, chronic gut inflammation causing reduced uptake, absorption and transportation of iron trans membrane, chronic and debilitating diseases, diseases of the endocrine glands like the thyroid and pancreas and various inherited disorders of metabolism can also cause anaemia [1, 2].

Table 1: W.H.O. Haemoglobin Thresholds used to define ANAEMIA: [1 gm/dl:0.6206mmol/L] [3]

Age/Gender Group	Haemoglobin Threshold [gm/dl]	Haemoglobin Threshold [mmol/L]
Child (Late Infancy and Early Childhood)	11.0	6.8
Child (Late Childhood to Pre Teenage)	11.5	7.1
Adolescence (Teenage)	12.0	7.4

About 0.5 g of iron is present as a reserve, in a full-term new-born as against of 5 g that is present in adults. Preterms have a still lower reserve. The body needs to absorb, on an average of 0.8 mg of iron, daily from the gut during the initial 15 years of life to meet the optimal requirements [4,5]. There are normal losses, in smaller quantity, where the additional amount of iron is necessary to overcome these losses of iron caused by shedding of cells from the G I tract. Thus, it necessitates absorption of nearly around 1mg of iron daily to maintain positive iron balance during childhood. Less than 10% of iron, from dietary sources is usually absorbed, and thus diet containing 8-10 mg of iron is necessary to be consumed on a daily basis, if dietary source is the only source, to maintain optimal iron levels.

Infancy which the phase of rapid growth, iron content from milk of animal sources and also from human breast milk is inadequate to maintain body iron levels to the optimum. Infants on exclusive breast feeding are always at an advantage in building iron stores, because they can absorb iron better and twice more efficiently than their counterparts who are fed cow milk. Breastfed infants, if are not weaned off and subsequently introduced to iron-fortified foods by six months of age, risk to land up in to iron deficiency [6] even if not IDA. In infants and toddlers with nutritional iron-deficiency anemia, the usual dietary pattern observed is that of excessive consumption of cow's milk [7, 8, 9] which has a low iron content, can cause loss of blood from the G I Tract as an effect or squeal of milk protein colitis). Under nutrition due to various social and cultural beliefs and reasons is also generally responsible for iron deficiency.

Differentiating Iron deficiency from iron-deficiency anaemia:

Deficiency of iron in the body may not necessarily terminate in iron deficiency anaemia. The condition where serum iron levels fall below the threshold levels i.e. 50 mg/dL but there is no onset of pathology of

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anaemia has not yet set off is termed as iron deficiency. Iron deficiency may also have other non-hematologic, mild to severe and sometimes long lasting systemic outcomes. Iron deficiency with or without iron-deficiency anaemia are associated with impaired neurological, limbic and cognitive functions during infancy[9]. Iron-deficiency anaemia may also be associated with, irreversible, cognitive defects[10]. There can also be an increased risk of precipitation of convulsive disorders, episodes of holding breath (BHS) in children, and exacerbations of restless legs syndrome[11]. Due to the potential of adverse neurodevelopmental outcomes, the goal of treatment showed be directed towards reducing the frequency of iron deficiency, throughout.

Diagnosing IDA [12]:

A complete and detailed medical and dietary history is important to diagnose any type of anaemia and iron-deficiency anemia in particular. A history of visits to areas where intestinal parasites like the hookworms and whipworms are endemic is helpful in conducting certain stool examinations for presence of parasites, cysts or their eggs and larvae[13].

As iron deficiency progresses in its course, biochemical and hematologic events occur sequentially. Iron stores deplete initially from the tissues due to varied reasons, and can be inferred by the reduced levels of serum ferritin. The iron-storage protein, ferritin, helps in estimating the iron stores in the body, in the absence of concomitant inflammatory pathologies[14]. Later the levels of iron in the serum also falls. The iron-binding capacity of the serum (serum transferrin) rises, and the saturation of transferrin falls to sub-normal levels. As iron level decrease, it becomes unavailable to generate haem as it cannot form a complex with protoporphyrin and at this point, iron deficiency culminates and progresses to iron-deficiency anemia[15].

With lesser hemoglobin, the size of red blood cells (RBCs) reduces, and they are termed as microcytes, and they also vary in size which is termed as anisocytosis. The changes are reflected as a decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH)[16]. The RBC count decreases. The percentage of circulating reticulocyte in the blood is mostly normal or slightly raised. The smear of peripheral blood shows hypochromic, microcytic RBCs with RBCs of various sizes. Iron-deficiency anemia is most of the times diagnosed by a complete blood count (CBC) showing a picture of microcytic anemia and with a high RDW (Reticulocyte Differentiation Width), decreased Hematocrit, normal Leucocyte count, and a normal or elevated thrombocytic count. Other biochemical investigative results like the reduced serum ferritin levels, reduced serum iron levels, and increased total iron-binding capacity (TIBC), generally, are not required unless the patient presents with a severe anemia or anemia requires a faster diagnosis for its cause, or other complications of anaemia are present, or the anemia does not respond to the conventional oral iron therapy. It is a challenging task to diagnose, in the absence of anemia, iron deficiency. For this, serum ferritin level is a useful tool, the value of which is increased, by also measuring C-reactive protein to help identify false-negative results because of associated inflammation.

Table 2: Differential diagnosis of microcytic anaemia based on laboratory parameters[16, 17]

Study	Iron Deficiency Anaemia	A or β Thalassemia	Anaemia of Chronic Disease
Haemoglobin	Reduced	Reduced	Reduced
Mean Corpuscular Volume	Reduced	Reduced	Normal / Reduced
RDW	Elevated	Normal / Minimally Elevated	Normal / Elevated
RBC	Reduced	Normal / Elevated	Normal / Reduced

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Serum Ferritin	Reduced	Normal	Elevated
TIBC	Elevated	Normal	Reduced
Serum Transferrin Saturation	Reduced	Normal	Reduced
FEP	Elevated	Normal	Elevated
Soluble Transferrin Receptor	Elevated	Normal	Normal
Reticulocyte percentage	Reduced	Normal	Normal / Reduced

The response to adequate administration of iron in iron-deficiency anaemia is important for diagnosis and is also a therapeutic indicator. Oral administration ferrous salts,[18, 19] is mostly economical and effective. No substantial evidence is available to prove the claim that the addition of trace metals, various vitamins, or other hematinic substance leads to any significant rise in the response of the body to simple ferrous salts. Calcium, dietary fibre are amongst the substances that are known to reduce the G I uptake of iron, but co-administration of ascorbic acid can overcome this. Tanin (tea and coffee) significantly inhibits absorption of iron.

The therapeutic dose of iron, to be administered orally, should be calculated in terms of elemental iron available from the ferrous salt used. Iron in a total daily dose of 3-6 mg/kg of elemental iron in a single or two divided doses is adequate as a daily regimen. Parenteral administration iron is considered for treatment in cases of malabsorption, where compliance to treatment is inadequate. As otherwise, oral iron therapy is effective, economical and safe. Iron therapy is known to increase the virulence of malaria and certain gram-negative bacteria and iron overdose is known to be mostly associated with Yersinia infection. Dietary counselling is usually effective. Consumption of cow's milk, needs be reduced significantly. There has to be an increment in consumption of iron through dietary items. Iron from haem sources is more bioavailable than from non-haem sources. Iron should be continued for 2-3 months after values of serum iron normalize, so as to replenish and re-establish iron stores.

Figs are an important source of various micro nutrients like vitamins, minerals, trace elements and macro nutrients like carbohydrates, sugars, and other compounds like phenolic etc.[20, 21]. Fresh as well as dried fruits of figs are a rich source of dietary fibre, sugars (carbohydrates), amino acids and polyphenols [22, 23]. In the traditional systems of medicine like as Āyurveda, Unānī, and Siddha figs have been quoted and are advised to be used to treat various diseases of the endocrine system, respiratory system, digestive system, and in females for disorders related to menstruation. As per data of USFDA, dehydrated figs are rich in fibre content, minerals like potassium, magnesium, manganese, calcium, copper, iron and vitamin K_3 (Phylloquinone). Fruits also are rich with other nutrients in smaller proportions. Fruits of Ficus carica (Figs) are known to have a comparatively lower content of cholesterol and fat but have an adequate amount of amino acids [23,2 4, 25, 26].

The fruits of Phoenix dactylifera Linn are called as Kharjūra in Āyurveda. In colloquial language they are called as Dates and they are considered to be rich in simple carbohydrates like sucrose, glucose and fructose which constitute to about 65% – 80% of carbohydrates, and are a high source of dietary fibre and certain essential minerals. Kharjūra or dates fruits, though have a low contain fats and proteins, they have a high sugar concentration and are devoid of any starch content. They are rich with of vitamins like niacin, pyridoxine, riboflavin, thiamine, pantothenic acid, minerals like manganese, magnesium, iron and even phosphorus. The fruits are also good source of biological forms of mineral compounds of zinc, copper, potassium, selenium and folic acid.

Dried black grapes (Vitis Vinifera) i.e Black Currant, are described as Drākśā in Āyurveda. Manganese is the

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important basic mineral constituent of grape. Currants contain vitamins like pyridoxine, thiamine, riboflavin, ascorbic acid and potassium. Analytical studies have shown that it also contains an organic chemical substance known as resveratrol, a polyphenol having antioxidant properties[27].

2. Methodology

An interventional study was conducted in an urban and semi urban area at two centers simultaneously. Ethical clearances were obtained from both the centers. Prior to the commencement of the trial and recruitment of patients, the trial was registered with the Central Trial Registry of India, after getting an institutional ethical clearance, and a trial number was obtained (CTRI/2019/10/021749). A fresh paste was prepared from dry figs, dates and black currants, 10 grams each, soaked in water overnight. Recruited children, suffering from IDA consumed the same for a span of 30 days, daily, during the early morning hours, empty stomach. The child had to undergo a haematological examination for assessment of a complete blood count, and also a biochemical assessment for levels of iron, ferritin and total iron binding capacity before the commencement and also at the end of the trial period. The blood investigations performed, prior to commencement of investigations helped in confirming the diagnosis of IDA and those at the end of the intervention were for the assessment of the effect of intervention.

3. Results and Discussion:

The data collected in the present study in respect of biochemical parameters are detailed below and were studied for improvement in individual factors and the results were subjected to statistical analysis.

Table 3: Effect of the interventional compound on Symptomatology of IDA

Parameter	Pre Rx Mean	Post Rx Mean	Difference	%age of improvement	'Z' value
Food aversion	1.95	0.625	1.325	67.95	-7.106
Anorexia	2.075	0.85	1.225	59.04	-7.289
Dysgeusia	2.1125	0.885	1.225	57.99	-7.289
Nausea	2.0	0.8215	1.1875	59.38	-7.173
Heaviness of the body	1.3375	0.525	0.8125	60.75	-6.031
Drowsiness/Lassitude	2.075	0.575	1.5	72.29	-7.06
Soreness of body	2.0375	0.6	1.4375	70.55	-7.379
Pallor	2.1125	0.575	1.5375	72.78	-72.68
Emaciation	2.0875	0.9125	1.175	56.29	-7.725
Loss of appetite	0.8375	0.6375	0.2	23.88	-3.771
Palpitation	2.1125	0.5375	1.575	74.56	-7.352
Liking for sour foods	2.0	0.4625	1.5375	76.88	-6.981
Cold aversion	2.0875	0.525	1.5625	74.85	-6.959

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Dryness	1.9875	0.4875	1.5	74.47	-6.914
Exhaustion on slightest exertion	2.0375	0.525	1.5125	74.23	-6.86
Lethargy/weakness	1.975	0.5375	1.4375	72.78	-6.835
Edema/Periorbital edema	1.9375	0.45	1.4875	76.77	-6.968
Sleep hours	1.9625	0.4875	1.475	75.16	-6.992
Restless Leg Syndrome	1.9375	0.425	1.5125	78.06	-7.027

The symptoms evaluated for IDA, in the patients, were mostly based on the patient history and also from the texts. The trial intervention had shown statistically significant effect in treating IDA in the form of reduction in the severity of the symptoms and improvement was observed persistently for all the symptoms, those were assessed. For all symptoms that were assessed, it was throughout observed, that the improvement/relief was much better with the use of trial compound. The trial compound was also effective in reducing the severity of symptoms faster, giving a faster and a lasting relief. The percentage of improvement seen was also significant as seen from the above observation table with significant fall in the means in all symptoms post treatment when compared to those of pretreatment. The high Z values, statistically confirm the findings that were observed clinically.

Table 4: Effect of Interventional Combination on Haematology and Biochemistry Parameters[29]

Parameter	**Haemoglobin**	**Serum Iron**	**Serum Ferritin**	**TIBC**
Mean Before Rx	7.95	35.06	17.38	535.88
Mean After Rx	10.05	70.8	39.71	339.25
X	2.10	35.74	22.33	196.63
Percentage of improvement	20.97%	50.48%	56.25%	57.96%
't' value	29.57	42.25	19.37	20.337

The mean of Haemoglobin on 1st day (pretreatment) was 7.94 which increased to 10.056 on the 30th day (at the end of treatment). The mean increment was 20.97% which was significant as calculated by the paired t test (as p value <0.05). Thus it can be said that there is significant increment of Haemoglobin. Increase in haemoglobin is not only dependent on supply of substarte iron; though iron has a major role to play in rise in haemoglobin, but also on supply on other nutrients as the molecule is made up of two contents; the haem and the globin. Dietary iron also has an influence on the rise in haemoglobin.

The mean Serum Iron on 1st day was 35.06 which increased to 70.8 on the 30th day. The mean increment score was 50.48% which was significant as observed again by paired t test (as p value <0.05). Thus it was inferred that there is significant increment in Serum Iron. This can, most likely be due to better absorption of iron from the interventional combination as it was in the form of biological form of iron.

The mean of Serum Ferritin on 1st day was 17.37 which increased to 39.71 on the 30th day. The mean increment in score was 56.25% which was again significant on

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calculation by the paired t test (as p value <0.05). Thus it can be said that there is significant rise in Ferritin levels. Ferritin also rises with inflammatory pathologies and so is considered to be an inflammatory marker. In this study, inflammation was not ruled out on serological parameters like measuring C-reactive protein, and so, it is difficult to comment whether there were any inflammatory conditions present in the subjects post completion of study, though visually, clinically or symptomatically there were none nor there were any reported conditions by the study subjects so as to suspect so.

The mean TIBC on the 1st day was 535.88 which decreased to 339.25 at 30th day. The mean decrement score was 57.96% which is significant as observed by paired t test (as p value <0.05). Thus it can be said that there is significant fall in TIBC. The fall in Total Iron Binding Capacity was consistent with the findings of rise in haemoglobin levels and also with rise in serum iron levels. The Total Iron Binding Capacity is inversely proportional to the serum iron levels and haemoglobin levels. Thus a fall in TIBC is indicative of rise in Haemoglobin.

4. Conclusions

The increment in haemoglobin and serum iron level concentration and total iron binding capacity is significant, though the haemoglobin has not reached the normal levels in the 30 days span. The increment of levels of ferritin is better. The trial combination does not give rise to any adverse/untoward/unwarranted reactions of the drug as are commonly seen with the commonly used iron salts.

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