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IRON DEFICIENCY ANEMIA;
SINGLE VERSES THREE TIMES DAILY DOSES OF FERROUS SULPHATE

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ABSTRACT...Introduction: The adherence to treatment of iron deficiency anemia often is poor in both developed and developing countries. The current standard therapy is oral ferrous sulfate administered 3 times daily. It is possible that adherence would improve with a single-dose daily treatment regimen. **Objectives:** To compare single versus thrice daily ferrous sulfate for treatment of iron deficiency anemia in young children. **Design:** Quasi experimental study Setting: Children Department Military Hospital Rawalpindi. **Period:** From (01 Jan- to31 Mar 05 and 03 Jul to 02 Oct 05) Subjects and Methods: Total 250 patients of iron deficiency anemia (hemoglobin values: 7.0 to 9.9 gm/dl and serum ferritin values: 10 ng/ml or less) were identified. Children divided into two groups and matched on the basis of age; and gender. One group (n = 125) received ferrous sulfate once daily and the control group (n = 125) received ferrous sulfate thrice daily at a total dose of 6 mg/kg/day of elemental iron for 2 months. Hemoglobin and serum ferritin values were measured as baseline and at the end of the study. **Results:** Successful treatment of anemia (target hemoglobin > 10 gm/dl) occurred in 81.42 % of the single dose and in 79.83 % of thrice daily dose groups and the side effects were minimal between the two groups. Conclusion: A single versus a 3 times daily dose of ferrous sulfate resulted in a similar rate of successful treatment of iron deficiency anemia, without significant side effects.

Key words: Iron, Anemia, ferritin.

INTRODUCTION

Hemoglobin level of less than 11 gm/dl and a serum ferritin level of 10 ng /ml or less are taken as iron deficiency anemia in 1–2 years of age[1-3]. Iron deficiency, the most common nutritional problem in the world, affects two thirds of children in most developing nations[4,5,6].

The global prevalence of iron deficiency anemia in young children is 43%. The Pakistan National Nutrition Survey found that 65% of children between the ages of 7–60 months were anemic[7]. According to a recent National Nutritional Anemia Survey, iron deficiency in children has accounted for 83% of all anemias[8].Absorption of about 0.8 mg of iron per day from the diet is required, of which

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0.6 mg is needed for growth, and 0.2mg to replace losses[3].

The total amount of iron absorbed by breast fed infants is less than that absorbed by those receiving an iron supplemented formula, and by 9 months, there is evidence of iron deficiency in some breast fed infants, unless additional sources of iron are present in the diet[9,10]. The early introduction of unmodified cows' milk as the major milk source at around 6months of age is the most common dietary characteristic of infants found to have IDA at 1year[11].

Other contributing factors considered to be responsible for iron deficiency anemia are low purchasing power of the people, low bio-availability of iron from cereal-based diets, poor dietary practices and poor hygiene and sanitation which increase the risk of infection and worm infestation.

At least 4 important variables may influence the success of treatment of iron deficiency anemia with oral iron: the dose per 24 hours, the frequency at which the dose is provided, the form in which the dose is provided, and the patient's adherence to treatment. The present criterion standard for treatment is 1.5 to 2.0 mg of elemental iron per kilogram of body weight provided 3-times per day (total dose: 4.5-6.0 mg/kg/d)[12].

The recommendation is to provide therapy for two months, then to enhance iron stores, to continue therapy for an additional one-month or more.

The adherence to treatment of iron deficiency anemia often is poor in both developed and developing countries. The current standard therapy is ferrous sulfate drops (or syrup) administered three times daily. It has been suggested that alternative treatment regimens and iron formulations may improve out come[13,14]. Sufficient studies from developing countries are lacking regarding the efficacy of different dosage regimen especially in Pakistan.

The purpose of my study is to compare the efficacy and to determine any difference in the outcome of treatment of iron deficiency anemia with single dose and three times daily dose of ferrous sulfate.

MATERIAL AND METHODS

Setting

The pediatric unit of military hospital Rawalpindi is 175 bedded and with a daily out patient department workload of approximately 250 patients.

Sample size

125 Patients in each group; total 250 patients

Sample technique

Non-probability convenience sampling.

Inclusion criteria

Age-six months to eighteen months. Children with Iron deficiency Anemia (Hemoglobin concentration between 7.0 gm/dl to 9.9 gm/dl & serum Ferritin level 10ng/ml or less than 10ng/ml)

Exclusion criteria

Children with severe anemia (Hemoglobin <7 gram/dl).
Preterm and low birth weight babies.
Malnourished & chronically ill patients.
Infants on Iron fortified Formula.
Children with chronic infections.

Children on long term drug therapy including Anti TB medicines. Excessive use of tea, foods containing Phytates, phosphates (strict vegetarians). Parents not wiling to include their children in the study.

Data collection

Total 250 cases of iron deficiency anemia were identified, which were divided into two groups containing 125 cases each. Children in both groups were matched mainly on the basis of age and gender. However socioeconomic status and severity of anemia was also considered in matching two groups, as caution was taken not to match two cases with wide difference in their Haemoglobin and serum ferritin at the time of start of treatment.

Detailed history including symptoms, systemic inquiry, birth, feeding, and immunization, past medical and

surgical, family and socioeconomic factors, along with thorough physical examination was done. After strict adherence to inclusion and exclusion criteria two groups, each comprising of 125 matched cases were included in the study.

The blood samples were obtained and analyzed in laboratory for base line investigations including Hb, TLC & DLC, red cell indices (using SYSMEX-KX-20 Analyzer), Retics (manually) count and serum ferritin (by IMMULITE Analyzer).

The cases were randomly divided in two groups according to two-treatment protocol. One group was treated by single daily dose of 06 mg / kg of oral iron and other group was treated by same daily dose divided in three doses per day.

The follow up was done fortnightly, and at each visit mother was questioned about the side effects and adherence to treatment during the preceding 14 days. The data collected about side effects included the incidence of diarrhea, constipation and general discomfort with iron syrup. The question about adherence to treatment included, whether the children objected taking the iron and how many doses were missed. More over hemoglobin and reticulocyte count was also checked fortnightly.

After completion of two months treatment with oral iron detailed evaluation was carried out including information regarding compliance, side effects of treatment, Hb, Retics and serum ferritin. On the basis of improvement in Hb concentration as well as of serum ferritin, results were determined and two groups were compared for efficacy. All the data was collected and recorded on a proforma (Annex A)

Data analysis

Data was analyzed using the statistical package SPSS version 10.0.Statistical significance of the hypothesis for comparing two treatment regimens was determined by paired t-test at 5% level of significance. The descriptive statistics like mean and standard deviation were calculated for age, hemoglobin and ferritin levels. Frequency and percentages were presented for gender.

The balance of baseline measurements across the interventions was examined. The effects of iron supplementation were analyzed on an intention-to-treat basis.

The change of hemoglobin as well as ferritin levels from pre- to post-treatment was examined and compared across the interventions (single daily dose verses three times daily dose of ferrous sulfate) using paired t-test. Independent sample t-test was used to compare the both groups for checking the effects of interventions. A P-value less than 0.05 was considered statistically significant.

RESULTS

After completion of two months of treatment with oral iron, detailed evaluation was carried out. For children who took drops (or syrup) three times-daily 84% received all of the prescribed doses compared with 86% in the once daily group. There was no difference in adherence to treatment between the children whose anemia did or did not resolve. Missing values were similar among groups. Seventy seven percent of mothers reported that their children objected to taking the drops (or syrup) in some way. Reported side effects were rare and mild and consisted mainly of diarrhea. There was no difference between the groups (diarrhea reported in16.8% of 3-times-daily group verses 16.3% in the once-daily group).

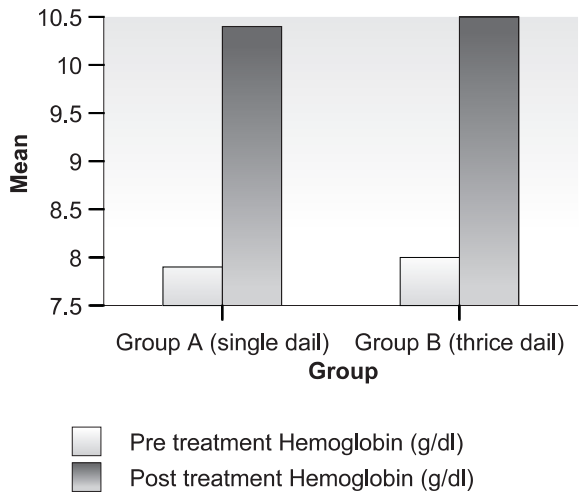
The primary outcome was significant rise in hemoglobin concentration in both groups (hemoglobin concentration > 10.0 g/dL). Twenty three children were absent from the study at the end of trial. This loss was distributed similarly between the treatment groups; moreover, there was no difference in baseline characteristics between these children and the rest who successfully completed the treatment trial. Consequently, a total of 227 children completed the second and final assessment, including blood sampling.

There was no significant difference in the mean age, hemoglobin, or ferritin values between the two treatment groups at the start of trial. Gender was represented about

equally between the groups.

In both groups, there was a significant increase in hemoglobin concentration from base line to the end of the study which was statistically highly significant (p<000). The change in hemoglobin concentrations was similar between two groups (Fig-1).

Fig-1. Pre and post treatment haemoglobin levels in Group A and B



About eighty percent (80.62%) children advanced from baseline hemoglobin to the target hemoglobin (values > 10 g/dl). This rate was similar between groups: 81.42% for the once-daily ferrous sulfate group and 79.83% for the three-times–daily group (table- I & II & Fig-1).

Table-I. Base Line Statistics (n = 227)

	Mean ±/S.D
Age of patients in months	10.9±03
Male : Female	119:104 (53:47%)
Pre treatment Hb (g/dl)	7.94±0.6
Post treatment Hb (g/dl)	10.2±0.7
Pre treatment ferritin (ng/ml)	9.0±2.4
Post treatment Ferritin (ng/ml)	24.4±06

The geometric mean ferritin values at baseline was similar in both groups, and there was a significant increase after two months of treatment (p<.000) in both groups (see table-I & III & Fig-2). There was no significant difference between the two groups for response to the two doses forms of iron administration.

Table-II. Mean Hemoglobin and Percentage Anemic by Treatment Groups at Baseline and After 2 Months of Treatment (n=227)

	Once daily dose (n=113)	03 times daily dose (n=114)
Baseline hemoglobin (g/dl)	7.92±0.51	7.96±0.54
Percentage anemic	100	100
Final hemoglobin (g/dl)	10.35±0.86	10.51±0.44
Percentage anemic	18.58	20.17

Fig-2. Pre and post treatment serum ferritin levels in Group A and B

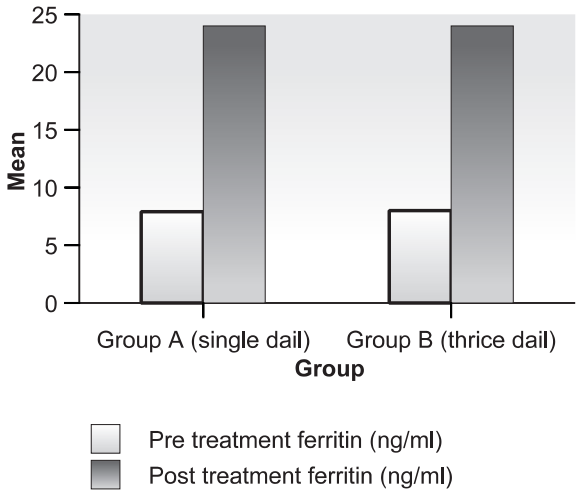
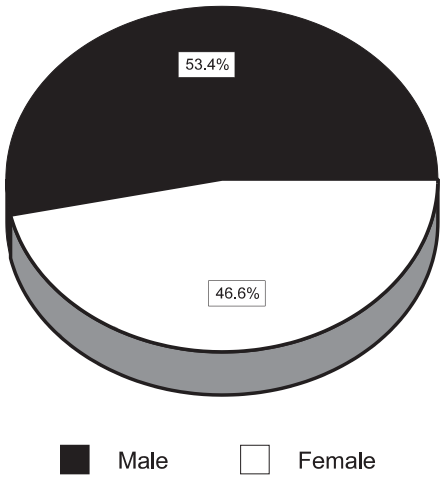


Table: III. Mean Ferritin Values, by Treatment Groups, at Baseline and After 2 Months of Treatment (n = 227)

	Once daily dose (n=113)	3 times daily dose (n=114)
Baseline ferritin (ng/ml)	8.64±2.1	8.89±2.7
Final ferritin (ng/ml)	24.50±6.3	24.69±4.5

Fig-3. Gender distribution (n=227)



DISCUSSION

Anemia can be caused by iron deficiency, folic acid deficiency, vitamin B12 deficiency, and other causes. Iron deficiency anemia is the most common preventable nutritional deficiency in the world, despite global goals for its reduction[15]. In the developed countries, iron deficiency anemia occurs to a lesser extent than in developing countries because of the higher consumption of red meat and the practice of food fortification (addition of iron to foods by the manufacturer). Decreased iron intake is a contributing factor in iron deficiency and iron deficiency anemia. In developing countries located in tropical climates, the most common cause of iron deficiency anemia is infestation with hookworm.

Although many developing countries recommend iron supplementation for pregnant women and young children and treatment of documented anemia, adherence to treatment often is poor. It has been suggested that alternative treatment regimens and iron formulations may improve outcomes[16,17]. Is once-daily iron as effective as three times daily in treating children with anemia? This concept has also been discussed previously.[18] Recently (in 2004) a study conducted by Biochemistry department of Ziauddin Medical University Karachi has compared mainly daily verses weekly iron supplementation in iron deficiency anemia[17]. For the same reason I compared once daily dose of Ferrous Sulfate with three times doses for the treatment of iron deficiency anemia in children aged 6-18 months.

In this study I selected the children of 6-18 month old because approximately 20-25% of all infants in the world have iron deficiency anemia, and many more have iron deficiency without anemia[11]. In my study when post-supplementation values of the biochemical parameters were determined, a significant improvement was observed in all parameters in both groups and both treatment arms resulted in similar increase in hemoglobin and ferritin from the beginning to the end of the study.

Any reported symptoms (abdominal discomfort, bloating, nauseas, diarrhea, or constipation) in previous weeks that may have been related to the iron supplement were also recorded. Parents were instructed to give the iron supplement with plenty of water (mostly one hour before meal) and not to give tea or coffee at that time so as to optimize iron absorption. During the fortnightly visits, when the parents were asked if the medicine had any effect on the sense of well-being of their children, majority of parents reported improvement in appetite.

Accordingly single daily dose is not too high to cause side effects and achieve better adherence compared with the standard 3 times daily dose. The risk of toxicity increases as the dose of elemental iron increases: doses more than 30 mg/ kg are potentially toxic and doses in excess of 180 mg/kg are potentially fatal. Our target dose of elemental iron was 6 mg/kg/day. Thus, 5 or > 30-fold over-consumption would be required to fall into the potentially toxic and potentially fatal categories, respectively. It seems unlikely that any of the children over-consuming iron in our study would have experienced serious adverse effects as a result.

There are a number of possible explanations for why nearly 20% of children remained anemic (target hemoglobin <10gm/dl) after two months of treatment. The history taken initially and during follow up revealed complaints of pica, worm infestation and some episodes of routine respiratory infections and gastroenteritis. Parasitic infections may have contributed to continuing

blood loss, thus causing refractory anemia, although all the patients with history of pica and worm infestation were de-wormed during this study. Moreover majority of children had a rural background and belonging to a lower socioeconomic group. Enquiry about pattern of feeding revealed that most of the mothers breast fed there babies wholly or partially while others preferred artificial feeding. However, the astounding observation was the practice of late introduction of weaning foods (one of most common causes of iron deficiency anemia).

For the past 150 years or more, oral ferrous sulfate has been the primary therapeutic (and preventive) source of iron for treatment of IDA[20]. When a soluble form of iron (e.g., ferrous sulfate) is ingested in proper dose, this intervention is effective. However, adherence to long-term ingestion of oral iron syrup (in an unsupervised setting) often is poor[21]. In fact; there is very little evidence of large scale effectiveness of iron supplementation in young children.

Various strategies to improve compliance have been explored. Some have focused on changing the formulation of iron to try and reduce the incidence of side effects, which are thought to contribute to poor compliance[22]. Other factors known to affect compliance include the motivation of those dispensing the drugs (all kinds of drugs including iron), their perceived safety and efficacy, their presentation, and the complexity of the dosing regimen. Finally, although hitherto unproven, it seems likely that inviting patients to return for a follow-up appointment, might also improve compliance.

Although the use of ferrous sulfate, even once daily, still is complicated by strong and unpleasant taste and the staining of teeth if the drops or syrup is not placed carefully at the back of the infant's mouth or the teeth are not immediately wiped, from a practical perspective, the option of using ferrous sulfate once daily may improve adherence to treatment and thus the success rate for the treatment of anemia. Better understanding of the regulation of iron metabolism and requirement during the critical early period of growth and development is needed for relevant control of iron deficiency anemia. As daily supplementation with iron is effective at improving iron status, this option should be thoroughly explored in the context of programs for the prevention and the treatment of iron deficiency anemia.

CONCLUSION

This study concludes that single daily dose iron supplementation is as effective as thrice daily supplementation for treatment of iron deficiency anemia. Moreover single daily dose is easier for both mother and children to comply with.

In developing countries like our country where economic resources are limited and curative services are not sufficient, preventive strategies are more important. There is a need of more and more concentration on some selected and feasible interventions to reduce the incidence of iron deficiency anemia.

RECOMMENDATIONS

Two major weapons to control IDA in developing countries are preventive measures and case management.

In the view of the findings in our study and other studies we suggest that:

Once-daily iron (6 mg/kg/day) appears to be comparable to thrice-daily iron in treating children with anemia. Once-daily iron therapy (6 mg/kg/day of elemental iron) is as effective as 3 times per day dosing in the treatment of children with iron deficiency anemia without an increase in side effects. Most parents (and probably their children as well) should prefer once-a-day dosing of medicine, which is supported by this study. Though there was no difference in compliance noted in this study, many other studies have shown that compliance increases as dosing frequency decreases.

Our evidence of intervention effectiveness predominantly relates to a small- scale efficacy trial, which may not reflect the actual effect under expected condition. Therefore a large scale multicenter National level trial in the context of treatment of iron deficiency anemia is required before it is implemented as National recommendations.

As iron deficiency anemia in infants and young children is known to have a negative impact on motor and socio-emotional development and cognitive function, further studies in this filed are required to find out more and more risk factors and preventive interventions to reduce the morbidity and cognitive dysfunctions caused by IDA.

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