Iron Deficiency Anaemia: Continuous Versus Intermittent Treatment in Anaemic Children

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Abstract

Iron deficiency anaemia is a common disorder among paediatric population. Traditionally, oral iron is given for treatment on daily basis. We undertook this study to compare the results of intermittent with continuous oral iron therapy in children. The study was conducted at Combined Military Hospital (CMH), Lahore. Children (aged 1 to 6) with iron deficiency anaemia (Hb 11 gIdl) were allocated at random into two groups, A (n=27) and B (n=28). The mean Hb of group A, before treatment, was 8.56 (±1.51) g/dl and that of group B was 8.32 (±1.68) gIdl. Group A was given daily oral dosage of 6 mgfkg of elementAL iron whereas group B was given the same dosage of iron but only 3 days a week. After 2 months of treatment the Hb of group A rose to a mean of 11.06 (±0.72) g/dl and that of group B was increased to 11.3 (±0.90)g/dl, respectively. The difference, in the rise of Hb of two groups, was not statistically significant. It was concluded that in our sample of population, the results of intermittent and continuous oral iron therapy, for iron deficiency anaemia in children aged 1 to 6 years, were identical (JPMA 48:269,1998).

Introduction

Iron deficiency anaemia (IDA) is a world wide problem. In paediatric age group (1-10 years), the major cause of anaemia is iron deficiency[1,2], however, a small percentage could be due to malarial parasites, chronic infections and haemoglobinopathies. The current prevalence rate of anaemia, in children of world at large, is 30%[3] and that of South East Asia is 7Ø%[4]. Exact figures regarding this condition are not available for Pakistan, but according to the National Nutritional Survey of 1988 the prevalence of anaemia in children was around 65%[5]. All these figures suggest that IDA is a world-wide problem but has widespread prevalence in South East Asia as well as in Pakistan.

The consequences of iron deficiency in paediatric population include reduced school performance, behaviour abnormalities, impaired motor development, poor growth rate[6-10] and defective immunity with recurrent infections[11]. However, most of these effects are reversible or atleast their progression can be checked by iron administration[7,12]. According to some authors, there may be a critical point in early childhood at which lack of iron may have a permanent deleterious effect on the brain[13] and an adverse outcome for congnitive function may not be reversible with treatment, after this stage. The treatment requires iron administration in the form of syrup or tablet. Preventive programmes in the community utilising food additives and health education regarding dietary habits have not been very promising[14]. It is easier to treat IDA than to prevent it. The oral forms of iron therapy, has problems of GI tolerance, compliance, teeth staining and others. Poor compliance with daily administration is a well known phenomenon. That is why supplementation programmes with other micronutrients, such as vitamin A have been successful as compared to iron. This vitamin does not require daily administration and has fewer side effects.

Recently, it has been reported that in anaemic rats the administration of iron supplements every third day was as effective in improving iron status as was daily supplement[15]. Similar results were reported

by other workers in Berkeley[16], in rats. They showed that absorption of iron decreased logarithmically in daily supplemented rats, whereas in intermittently supplemented rats absorption decreased slowly and linearly.
Theoretical explanation is not adequate but it appears that iron supplementation timed to match mucosal renewal is more efficient. If this holds true for humans, it could have tremendous implications on therapeutic regimens for iron therapy. The aim of this study was to find out whether thrice weekly supplementation of oral iron would improve haernoglobin level as effectively as daily supplementation, in children with iron deficiency anaemia.

Patients and Methods

This study was conducted at Paediatric Department, Combined Military Hospital, Lahore, from January, 1996 to June, 1996. The subjects were children of both sexes, ranging from one to 6 years of age, attending outpatient departrnent with haemoglobin level of less than 11 g/dl. After a thorough history, physical examination was carried out by one of the doctors and a questionnaire was filled up with relevant infonnation. At the beginning of the study, 2 ml blood was drawn from each subject, by venipuncture. This was added to two bottles, one containing EDTA and anotherplainbottle, for haemoglobin and ferritin analysis, respectively. Haemoglobin was determined on computerised analyser Sysmex K-800 which was calibrated and standerdized every day. Blood indices (MCV, MCH & MCHC) and RBC morphology was also detenrnned in addition to haemoglobin estimation. Blood inplainbottles was storedforferritinanalysis, whichwas done at a later date by immuno enzymatic assay (magnetic solid phase) technique, for which commercial kits of Sereno diagnostics were used and controls were run with each batch of samples {calibrated after WHO first international reference preparation (IRP) for human liver ferntin 80/602}. Haemoglobin electrophoresis, bone nmrrow examination and other relevant tests were carried out, where required, in doubtful cases.
Children showing microcytic hypochroniic anaemia with blood indices suggestive of IDA (Hb <11 g/dl, MCV <70 fi, MCHC <20pg/dl) were included for further treatment. Subjects having macrocytic anaemia, haemoglobinopathies and other RBC disorders were excluded from the study at this stage. Moreover, all the children with any major illness (as pneumonia, gastroententis, malaria) in the past one month, children with chronic illnesses (including grade 3 malnutrition and malabsorption) and subjects already on anti anaemics were also excluded from the study.
One hundred and thirty childrenwere recruited (afterthe exclusion criteria) in the beginning and verbal informed consent was taken from the parents. All the children were dewormed at the start of the study. These children were allocated, at random, into 2 categories. Group A was control group ad Group B was the study group. Group A was given 6 mg/kg/day of elemental iron (ferrous gluconate syrup), once daily for two months. Group B was also given 6 mg/kg/day ferrous gluconate syrup), but only on three consecutive days a week, again for two months. Repeat blood examination for haemoglobin estimation was carried out after 2 weeks of iron therapy, to see adequacy of response, as this is still a reliable way to diagnose IDA17. All the patients were seen by the doctor at two weeks and 8 weeks duration, to assess about the compliance of medication and to register any other illness or problem during this period.
Data analysis was carned out by using software package SPSS/PC +4 6 (SPSS Inc, Chicago) with the two treatment types (daily vs thrice weekly supplementation) as a between subjects factor and treatment effect (before vs after supplementation) as a within-subjects factor.

Results

The study was started with 130 children initially but only 55 (45%) could complete the treatment, due

to the reasons shown in Figure.

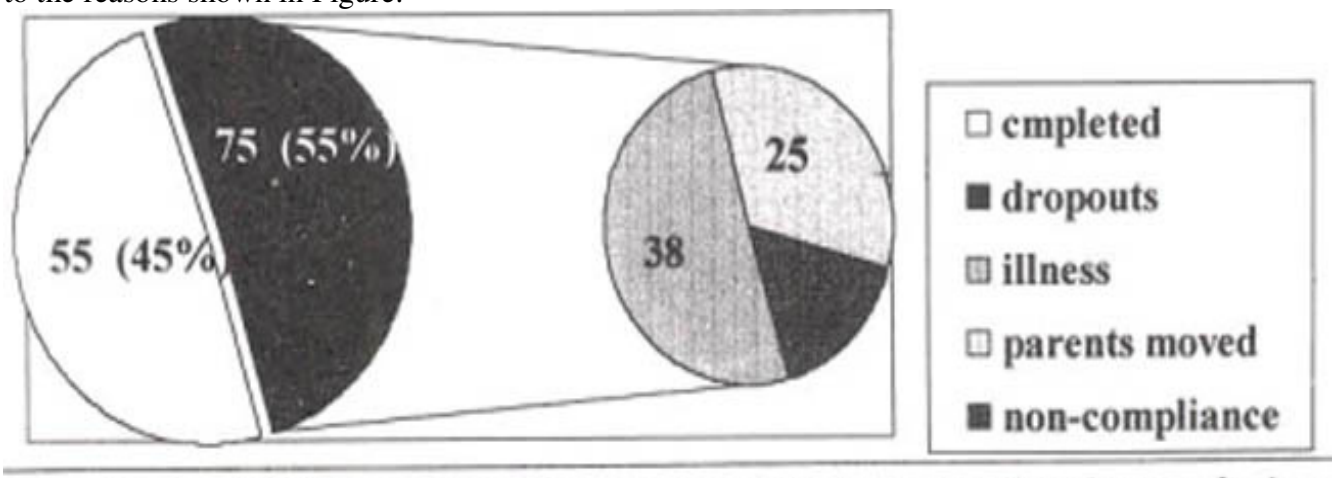

Figure. Number of children (percentage in brackets) participating in the study and reasons for drop-outs.

Thirty-eight subjects developed a major illness as malaria, gastroenteritis, typhoid or pneumonia during this period. As transfers and postings are common in this community, a large chunk of 25 children moved to other cities and thus were not able to finish the treatment. A complete set of data was obtained for 27 children in group A (on daily treatment) and for 28 children in group B (on thrice weekly treatment). In the final data set no significant difference was noted in the age and sex distribution of both groups. The average age for group A was 27.04 months and that of group B was 26.25 months (P=0.79).

At the start of the supplementation there was no significant difference in the meanvenous blood haemoglobins of group A and B, as shown in Table I (P=0.349, between subjects factor). The daily supplementation and thrice weekly supplementation, led to a significant increase in haemoglobins of both groups, estimated at the end of the treatment (P=0.05, within subjects factor). The Hb in group A increased from a mean of 8.56 g/dl to 11.06 g/dl and that in group B from 8.32 g/dl to 11.3 g/dl. The final haemoglobin concentration of two groups is shown in Table I.

Table I. Comparison of haemoglobins before and after treatment.

	Group A (n=27)		Group B (n=28)	
	(Range)	Mean±SD	(Range)	Mean±SD
Initial	(3.2-1.09)	8.56±1.51	(4.5-10.9)	8.2±1.62
After treatment	(8.9-12.4)	11.06±0.72	(9.3-13.4)	11.3±0.90

The difference between the two is not significant (P=0.25, between subjects factor). The effect of treatment on two groups was also assessed by comparing the mean rise in haemoglobin concentration (2.49 g/dl and 2.48 g/dl for group A and B respectively), with treatment. The difference in ,two groups was not significant (P=0.346, between subj ccts factor).

Ferritin levels could be done in 44 (80%) children only, because of limited availability of the assay kits. A few children who had acute infections at the time of vempuncture, showed a false rise in serum femtin level and had to be excluded from the analysis. The mean initial ferritin, for group A was 9.77 ng/dl and that of group B was 9.73 ng/dl (P=0.62, between subjects factor). After treatment, the mean final level of 23.5 ng/dl for group A and 19.6 ng/dl for group B was noticed (P=0.385, between subjects factor). The other indices measured before and after the treatment also showed similar trends, as shown in Table II.

Table II. Comparison of mean values of various blood indices before and after the completion of study.

	Group A (n=27)				Group B (n=28)			
Indices Units	MCV (f/l)	MCH (p/g)	MCHC (g/dl)	PCV (%)	MCV (f/l)	MCH (p/g)	MCHC (g/dl)	PCV (%)
Initial	61.7	19.18	30.91	0.28	58.52	18.2	30.30	0.27
Final	72.28	23.96	32.95	0.33	70.96	23.5	32.9	0.34
Difference	10.51	4.78	2.04	0.05	12.44	5.3	2.65	0.06

P value of all the indices was >0.1

Sixty-six percent children in group A and 71% children in group B (P=0.29) achieved a Hb of more than 11 g/dl during the course of treatment. Only 25% subjects developed teeth staining during oral iron therapy in 40.7% in group A.

Discussion

In the present study a complete set of data was obtained in 55 subjects only. We started off with 130 children but 45% could complete the study. Fifty five percent dropped Out because of various reasons, about 28% due to one or other illness as pneumonia, typhoid and gastroenteritis and 27% due to non specific causes as transfer of parents, failure to follow up at arranged appointments and failure to take medicines as instructed. This high drop out rate is not unusual in our region as people often fail to comply with doctor's instructions and are irregular in visits to hospitals.

The haemoglobin levels of both groups showed a significnat improvement with treatment, which was comparable to each other. Similar results have been obtained by other workers in children from Indonesia[18]. Studies have been carried out in adult population and the rise of Hb was found to be comparable between continuous and intermittent regimem[19]. This regimen of intermittent therapy originated from works on rats, in which the iron supplementation was timed with intestinal inucosa renewal period and the results indicated that continous therapy had no advanatagc over this form of treatment[15,16] . Our study supports these observations. With intermittent dosage the level of absorption remains high. whereas with daily dosage the level of absorption decreases rapidly after a few days[16]. Assuming that young children have 75 ml blood volume/kg body weight and that one gin hacmoglobin has 3.4 mg Fe20. A calculation was made that the amount of absorbed iron, to accountjust for increase in Hb in blood circulation, was 5.4% in the group supplemented thrice weekly and 2.11%, in the group supplemented daily. This clearly indicates, the better utilisation of intermittently administered iron as compared to daily supplementation.

These figures are comparable to those expressed by the workers, ma similar study, on intermittent and continuous iron therapy in children[18].

Blood indices (MCV, MCH, MCHC) other than Hb also showed a significant improvement after treatment, which was comparable in both the groups. Serum Ferritin correlated well with the haemoglobin level at the initiation of the therapy (excluding the patients who had acute infection). However the rise was not as much as the rise in Hb was observed, with treatment. This Was expected as treatment of iron deficiency anaemia does not cause a significant rise in ferritine evels, until normal Hb levels are achieved[21].

The initial number of children recruited in group A was 70 and that in group B was 60. The compliance rate was much better in group B as we could complete the data in 28 subjects in this group as compared to 27 in daily regimen group. The gastrointestinal side effects were also less in intermittent therapy group. Four patients in group A and one ingroupB had to have a change of once daily regimen to thrice

daily dosage scheme because of loose motions and gastrointestinal upset, however these cases were excluded from the study. More teeth staining was observed in group A as compared to group B. Hence, as is obvious that although therapeutic effects of therapy were comparable in both groups the incidence of untoward effects were less and compliance was better in group B.

In countries where IDA is a public health probelm various strategies have been applied to control the situation. Distribution of iron tables and fortification of staple diets have produced variable results in various communities. The major problem encountered with these programs is poor compliance (particularly with oral form of iron tablets and svrups) as they have to be ingested regularly for a relatively longer period. This is in contrast to other supplementations, as that of vitamin A. which is taken only once in a long period. Fortification of staple food has been relatively successful in countries[22], but it is very costly. Similarly, the role of dietary education in prevention of IDA is also not encouraging[14]. Keeping all the above tacts m mma, we need a regimen, which has better compliance, lesser side effects and is economical, for the population suffering from IDA. Intermittent therapy has all these benefits and is particularly economical as compared to continuous therapy.

It is concluded supplementation at less frequent intervals, such as once per week should be investigated. The optimal dosage, which may be much lower than we had used, should be sought and the most appropriate form of supplement (cost, tolerance and effect wise) should also be further looked into.

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