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COMPARISON OF EFFICACY OF IRON VS. IRON & VITAMIN-A COMBINATION IN IRON DEFICIENCY ANEMIA

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ABSTRACT

Objectives To compare the efficacy of iron vs. iron and vitamin A combined in the management of iron deficiency anemia in children

Methodology The children were allotted either group A or B according to their enrollment number in the study. Group A was the supplemented group and were given iron and vitamin A, while Group B was the placebo group and were given iron and a placebo. The patients were blind with respect to vitamin A and placebo.

Results In group A, mean hemoglobin was 8.28 gm% at enrolment and at the end of three months of follow up it was 10.02 gm%. The difference was of 1.74 gm% and range was from -0.6 to 4.8 gm% .In group B mean hemoglobin was 8.45 gm% at the beginning of the study and 10.14 gm% at the end of three months of follow up. The difference was of 1.69 gm% and ranged from 0.1 to 4 gm%.

Conclusion. Simultaneous administration of vitamin A along with iron showed a small difference in the rise of hemoglobin in preschool children. Despite intensive efforts by the government and private sector to improve hemoglobin and vitamin A status of children, much more needs to be done. New treatment strategies should be developed which might reduce the duration of oral iron therapy required to treat iron deficiency anemia.

KEYWORDS : HEMOGLOBIN ; VITAMIN-A ; IRON DEFICIENCY ANEMIA

INTRODUCTION

Iron deficiency, and iron deficiency anemia remains one of the most severe and important nutritional deficiencies in the world today. Every age group is vulnerable. Iron deficiency impairs the cognitive development of children from infancy through adolescence. It damages immune mechanisms, and is associated with increased morbidity rates. [1]

During pregnancy iron deficiency is associated with multiple adverse outcome for both mother and infant, including an increase risk of haemorrhage, sepsis, maternal mortality, perinatal mortality and low birth rate.[2]

This hospital based study was carried out to compare the efficacy of iron vs. iron and vitamin A combined in the management of iron deficiency anaemia in preschool children with mild to moderate anaemia and to find out whether this can reduce the duration of oral iron therapy required to treat iron deficiency anaemia, thus reducing the cost of treatment and also improving compliance.

Iron deficiency is one of the leading risk factors for disability and death worldwide, affecting an estimated 2 billion people. Nutritional iron deficiency arises when physiological requirements cannot be met by iron absorption from diet. Dietary iron bioavailability is low in populations consuming monotonous plant-based diets. The high prevalence of iron deficiency in the developing world has substantial health and economic costs, including poor pregnancy outcome, impaired school performance, and decreased productivity. [2,3]

Recent studies have reported how the body regulates iron absorption and metabolism in response to changing iron status by upregulation or downregulation of key intestinal and hepatic proteins. Targeted iron supplementation, iron fortification of foods, or both, can control iron deficiency in populations. Although technical challenges limit the amount of bioavailable iron compounds that can be used in food fortification, studies show that iron fortification can be an effective strategy against nutritional iron deficiency. Specific laboratory measures of iron status should be used to assess the need for fortification and to monitor these interventions. Selective plant breeding and genetic engineering are promising new approaches to improve dietary iron nutritional quality.[4,5]

Even with adequate counseling, the parents may not comply with the advised treatment. Early identification of anemia by clinical markers such as pallor goes a long way in detecting anemia in apparently healthy children.New treatment strategies should be developed which might reduce the duration of oral iron therapy required to treat iron deficiency anemia. More studies are needed in this area to establish the efficacy of additional vitamin A supplemen ntation in the treatment of iron deficiency anemia.[6]

METHODOLOGY

Study Type: Present study was a hospital based, prospective, randomized, single blind, placebo controlled and interventional study. The study protocol was approved by our Institutional Ethics Committee.

Population under study: Both boys and girls between the ages of 6 months to 5 years attending the outpatient department or admitted in the inpatient department of the Department of Pediatrics PCMS and RC with mild to moderate anemia due to iron deficiency were the target population for this study. This study was conducted from 1st November 2011 onwards for a period of 1½ years. The children in whom the diagnosis of iron deficiency anemia was established on the basis of history, examination, complete blood picture and serum ferritin level and who fulfilled the inclusion criteria were then enrolled into the study after their parent's consent.

Study Design: The children were allotted either group A or B according to their enrollment number in the study. Group A was the supplemented group and the children of Group A were given iron and vitamin A, while Group B was the placebo group and children of Group B were given iron and a placebo. The patients were blind with respect to vitamin A and placebo.

Inclusion Criteria:

1.	Age	-	6 months to 5 years
2.	Hemoglobin	-	Between 7 – 11 g/dL
3.	MCV	-	< 80 fL
4.	Ferritin	-	< 12 ug/L

Exclusion Criteria:

1. Severe anemia (hemoglobin less than 7 g/dL)
2. Overt signs of Vitamin A deficiency
3. Hereditary hemolytic anemia
4. History of vitamin A intake in the past 6 months
5. Any chronic systemic illness

Interventions:

1. Iron supplementation - 3mg/kg single daily dose (Iron Ascorbate), 1 hour before meals at home. Vitamin A as a stat dose at enrollment as direct observed therapy -

100000 IU to children < 1 year age & < 8 kg weight
200000 IU to children > 1 year age & > 8 kg weight

2. Universal deworming -

Albendazole at the beginning of the study as direct observed therapy to every child participating in the study.

1-2 years - 200mg stat dose
2-5 years - 400mg stat dose

After 6 weeks of taking the iron supplement the children were called for repeating the complete blood picture and then at the end of the study at 12 weeks also for the repeat complete blood picture. The data collected by the end of 12 weeks of follow up was analyzed by IBM SPSS 20 (Statistical Package for the Social Sciences - Statistical Software). The main criterion for status of anemia at the end of the study was hemoglobin rise.

OBSERVATION TABLES

At the end of sample collection 213 children were enrolled into the study. Out of these, 162 (76.1%) children completed the 12 weeks of study while 51 (23.9%) children could not be followed up as per the study design and were therefore excluded from the analysis.

There were 81 children in group A and 81 children in group B. In total there were 104 males and 58 females in this study. There were 56% (46) males and 44% (35) females in group A while there were 71% (58) males and 29% (23) females in group B.

TABLE 1: NUTRITION STATUS AND THE DEGREE OF ANEMIA

NUTRITION STATUS	GROUP A (Iron + Vitamin A)			GROUP B (Iron + Placebo)		
NO MALNUTRITION	49	MILD ANEMIA	04	51	MILD ANEMIA	04
		MODERATE ANEMIA	45		MODERATE ANEMIA	47
MODERATE MALNUTRITION Weight for height between -2 and -3 Z-score	32	MILD ANEMIA	04	30	MILD ANEMIA	03
		MODERATE ANEMIA	28		MODERATE ANEMIA	27

Table shows that, out of the 81 children in group A, 32 suffered from moderate malnutrition. Among these 32 children, 4 had mild anemia and 28 had moderate anemia. 49 children in group A did not have malnutrition. In these 49 children, 4 had mild anemia and 45 had moderate anemia.Out of the 81 children in group B, 30 suffered from moderate malnutrition. Among these 30 children, 3 had mild anemia and 27 had moderate anemia. 51 children in group B did not have malnutrition. In these 51 children, 4 had mild anemia while 47 had moderate anemia.

TABLE 2 - TREATMENT OUTCOME

Group	Degree of anemia on enrolment	Number of children	Hemoglobin at end of study		
			Normal	Mild anemia	Moderate anemia
A	Mild (Hb 10 - 10.9)	08	07	00	01
	Moderate	73	18	32	23
	Hb 9 - 9.9	17	11	06	00
	Hb 8 - 8.9	20	04	13	03
	Hb 7 - 7.9	36	03	13	20
	Total	81	25	32	24
B	Mild (Hb 10 - 10.9)	07	06	01	00
	Moderate	74	18	24	32
	Hb 9 - 9.9	23	14	08	01
	Hb 8 - 8.9	27	03	07	17
	Hb 7 - 7.9	24	01	09	14
	Total	81	24	25	32

Out of the 81 children belonging to group A (vitamin A and iron), 8 (9.8%) had mild anemia and 73 (90.2%) had moderate anemia. Out of the 8 children with mild anemia, 7 achieved a normal hemoglobin at the end of the study. Out of the 73 children with moderate anemia, 18 (24.6%) achieved a normal hemoglobin, 32 (43.8%) improved to mild anemia and 23 (31.6%) still had moderate anemia at the end of the study. In total, out of the 81 enrolled children, 25 (30.8%) had a normal hemoglobin at the end of the study in group A and majority of them had a higher hemoglobin (9 - 10.9 gm%) to begin with.

TABLE 3- PERCENTAGE MEAN HEMOGLOBIN RISE

	Group	N	Mean
%Hb rise at 6 Weeks	Vitamin A + Iron	81	12.7134
	Iron	81	10.9164
%Hb rise at 12 Weeks	Vitamin A + Iron	81	24.5535
	Iron	81	21.0264

Table shows the percentage of hemoglobin rise in the two groups at the end of 6 weeks and at the end of 12 weeks of study. The mean percentage hemoglobin rise in the group A (iron and vitamin A) was 12.7% at the end of 6 weeks and was 24.5% at the end of 12 weeks of study. In group B (iron plus placebo), the mean percentage hemoglobin rise was 10.9% at the end of 6 weeks and 21% at the end of 12 weeks of study.

TABLE 4: STATISTICAL SIGNIFICANCE OF PERCENTAGE RISE IN HEMOGLOBIN BETWEEN GROUP A (IRON PLUS VITAMIN A) AND GROUP B (IRON PLUS PLACEBO)

STUDY INTERVAL		Levene's Test for Equality of Variances		t-test for Equality of Means
		F	Sig.	T
%Hb rise at 6 Weeks	Equal variances assumed	.911	.341	1.357
	Equal variances not assumed			1.357
%Hb rise at 12 Weeks	Equal variances assumed	1.921	.168	1.753
	Equal variances not assumed			1.753

RESULTS

Out of the 81 children belonging to group B (iron and placebo), 7 (8.6%) had mild anemia and 74 (91.4%) had moderate anemia. Out of the 7 children with mild anemia, 6 achieved a normal hemoglobin at the end of the study. Out of the 74 children with moderate anemia, 18 (24.4%) achieved a normal hemoglobin, 24 (32.4%) improved to mild anemia and 32 (43.2%) still had moderate anemia at the end of the study. In total, out of the 81 children enrolled, 24 (29.6%) had a normal hemoglobin at the end of the study in group B and majority of them had a higher hemoglobin (9 - 10.9 gm%) to begin with.

STASTISTICAL ANALYSIS

There is no statistical difference between the two groups at the end

of 6 weeks and at the end of 12 weeks of study in terms of hemoglobin rise, when the t-test is applied (P value is more than 0.05 in either case).At the end of the study, all children except 1 had a rise in hemoglobin level. A total of 49 children out of 162 achieved a normal hemoglobin of more than or equal to 11 gm%. Out of these, 25 were from group A (iron plus vitamin A) and 24 were from group B (iron plus placebo).

DISCUSSION

The majority of children in the present study were from the age group of 6 to 18 months. This is in accordance with the NFHS-3 data which states that the highest prevalence is among the group of 6 to 23 months of age. Other workers have also reported similar results. Factors such as delayed starting of complimentary feeding, faulty feeding practices, recurrent infections and infestations that are common in this age group which may reflect the higher occurrence of anemia in this age group as seen in this study also.[1]

In the present study, a male preponderance was observed in both the groups despite randomization. This could possibly reflect a gender bias so deeply rooted in the minds of people in our society due to which they do not seek medical advice for female children unless they are seriously ill.

On correlating the nutritional status of children to the degree of anemia it was observed that 100 children (61.7%) in both the groups of normal nutritional status were found to be anemic of which 92 (92%) had moderate anemia and 8 (8%) had mild anemia. This is an important observation as apparently healthy children may also be anemic due to various reasons such as faulty feeding practices, poor complimentary feeding, prolongation of physiological anemia due to low iron stores, infestations etc. It is this group in which the parents find it difficult to perceive that their child has a problem which requires a long term treatment for 3 months or even longer.

In the present study 38.7% of the compliant children in group A (iron + vitamin A) and 34.7% in group B (iron plus placebo) had a normal hemoglobin at the end of the study. There were only 26% of the non-compliant children in group A and 21.8% of the non-compliant children in group B who had a normal hemoglobin at the end of the study period. Only one child showed worsening of anemia from mild to moderate who belonged to the non-compliant group.

In the present study, a rise in hemoglobin was observed in majority of children belonging to both the groups A and B. But a normal hemoglobin was achieved predominantly by those children who had a relatively higher hemoglobin to begin with. In those children with hemoglobin between 10 – 10.9 gm%, almost all had a normal hemoglobin at the end of the study period. In children with hemoglobin between 9 - 9.9 gm%, 62 had a normal hemoglobin at the end of the study. In those children with hemoglobin between 8 – 8.9 gm%, 15% had a normal hemoglobin at the end of the study and in those children who had a hemoglobin between 7 – 7.9 gm% at the beginning of the study, only 4% had a normal hemoglobin at the end of the study. An even longer duration of therapy might be required in these children.

In the present study, the mean hemoglobin at enrollment was 8.28 gm% while at the end of three months of follow up it was 10.02 gm% (increment of 1.74 g/dL, range – 0.6 to 4.8) in group A which was supplemented with vitamin A in addition to iron. While in group B which received iron and a placebo, it was 8.45 gm% at the beginning of the study and 10.14 gm% (increment of 1.69 g/dL, range 0.1 to 4) at the end of 3 months of follow up. There was no statistical difference between the two groups in our study. This was in contrast to some of the previous studies which showed improvement in hemoglobin status with vitamin A supplementation.

Mejia and Arroyave in 1982 in their study of the effect of improvement in vitamin A status on biochemical indicators of iron nutrition after vitamin A fortification of sugar found that vitamin A fortification had a favorable effect on iron metabolism. Muhilal et al. in 1988 in their study among preschool children in West Java, Indonesia demonstrated that hemoglobin concentration among children supplemented with vitamin A fortified monosodium glutamate increased by 1.0 g/dL after 5 months; (P<0.001), without any significant change in control group. Iron supplements were not given in the two groups. Both these studies showed that vitamin A has a favorable effect on iron status. [3,4]

In their placebo-controlled trial among anemic Guatemalan children, Mejia and Chew in 1988 showed an increase in hemoglobin concentration by 0.9 g/dL compared with an increment of 0.3 g/dL in the placebo group with daily vitamin A supplements for two months . In their study they had supplemented vitamin A 10000 IU daily for 2 months. Similarly, in a clinical trial on preschool children with clinical and sub-clinical vitamin A deficiency Semba et al. in 1992 75 showed that mega dose of vitamin A supplementation (200 000 IU) was associated with a significant increase of 2.1 g/dL haemoglobin among those children.[5,6]

Tanumihardjo et al. in 2004 conducted a study aimed at investigati ng the improvement in hemoglobin and vitamin A status in preschool Indonesian children following supplementation with vitamin A and deworming. The study showed that supplementation of vitamin A alone without iron increased hemoglobin levels and decreased anemia prevalence. Dreyfuss ML et al studied hookworms, malaria and vitamin A deficiency contribute to anemia and iron deficiency among pregnant women in the plains of Nepal [7,8]

In the present study children with overt signs of vitamin A deficiency were excluded. Bloem et al. in 1990 had found significant increments of hemoglobin after 2 weeks in children who were given a single initial dose of 200000 IU of vitamin A, but their study only included children with conjunctival xerosis. So the results cannot be compared.[9]

In a similar study by Giovannini M et al did a double-blind, placebo-controlled trial comparing effects of supplementation with two different combinations of micronutrients delivered as sprinkles on growth, anemia, and iron deficiency in Cambodian infants. They concluded that both MMN and FFA supplements were effective for preventing or treating anemia in Cambodian infants and stabilizing plasma levels of ferritin. Use of micronutrients in a controlled home setting, as sprinkled daily supplements, may be promising in preventing and treating anemia in developing countries.[10]

In a recent study Soekarjo et al. in 2004 found no effect on hemoglobin concentration by weekly vitamin A supplementation (10000 IU) and iron (60 mg) daily for a total of 14 weeks among schoolchildren in rural and urban East Java, Indonesia . Although similar results were observed in the present study also, but their study included only adolescents while the present study had only preschool children. The age group studied is different in the two studies. The cause of iron deficiency anemia is different in these age groups and other coexistent factors are also different.[11]

Results of the present study are comparable to a study done by Mwanri et al. in 2000 on 136 anemic school children. These children were divided into 3 groups - group 1 received only vitamin A, group 2 received only iron and group 3 was given both vitamin A and iron. All supplements were given for 3 days per week for 3 months. They found increments by 1.35 g/dL in hemoglobin concentration among children given vitamin A alone; in the group given iron alone the hemoglobin increased by 1.75 g/dL; and in the group given both vitamin A and iron the hemoglobin increased by 1.85 g/dL. In the present study, increase in hemoglobin in group A (iron + vitamin A) was of 1.74 gm% and in group B (iron + placebo) it was 1.69 gm% at the end of 3 months.[12]

Therapy with combined vitamin A and iron lead to a slightly higher hemoglobin rise in this study as compared to therapy with iron

alone, however, this rise was not found to be statistically significant. Mwanri et al. found a statistically significant difference in the hemoglobin rise in the two groups treated with vitamin A plus iron versus iron alone. Possible reasons for the effect vitamin A has on hemoglobin rise include enhanced iron absorption in the intestine , reducing the inhibiting effect of polyphenols and phytates on iron absorption and effective release of iron from liver and spleen to the bone marrow for erythropoiesis . The beneficial effects of vitamin A therapy on iron metabolism have been seen more in vitamin A deficiency states . In this study children with vitamin A deficiency were excluded and it is possible that the beneficial effect of vitamin A therapy though seen in this study but was only to a lesser extent as none of the study subjects had clinical vitamin A deficiency.[12]

In a similar study by Lozoff B et al who studied long-term developmental outcome of infants with iron deficiency , all the children had excellent hematologic Status and growth at five years of age. However, children who had moderately severe iron-deficiency anemia as infants, with hemoglobin levels ≤100 g per liter, had lower scores on tests of mental and motor functioning at school entry than the rest of the children. [13]

The World Health Organization is revising global guidelines for controlling IDA. Implementation of anemia control programs in developing countries requires careful baseline epidemiologic evaluation, selection of appropriate interventions that suit the population, and ongoing monitoring to ensure safety and effectiveness. This review provides an overview and an approach for the implementation of public health interventions for controlling IDA in low- and middle-income countries, with an emphasis on current evidence-based recommendations.[14]

CONCLUSION:

Out of the 162 children who completed the study period of 12 weeks, 81 received iron and vitamin A (group A) and 81 received iron plus placebo (group B). Half of the children in this study belonged to the age group of 6 – 18 months and a male preponderance was observed. A total of 100 children (61.7%) of normal nutrition status in both the groups were found to be anemic of which 92 (92%) had moderate anemia.

It was an important observation of this study that 61.7% apparently healthy children of normal nutritional status were found to be anemic of which 92% had moderate anemia Health care providers dealing with children should be aware of this and make use of this simple clinical marker for early detection and therapeutic intervention for iron deficiency anemia in children. Parents of all infants and preschool children at each contact with the health care provider even if it is for immunization should receive nutrition education regarding timely and appropriate complimentary feeding and correct feeding practices Despite intensive efforts by the government and private sector to improve hemoglobin and vitamin A status of children, much more needs to be done. New treatment strategies should be developed which might reduce the duration of oral iron therapy required to treat iron deficiency anemia. Simultaneous administration of vitamin A along with iron showed a small difference in the rise of hemoglobin in preschool children although this difference was not statistically significant. More studies are needed in this area to establish the efficacy of additional vitamin A supplementation in the treatment of iron deficiency anemia.

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