'Effectiveness of liquid iron alone and iron with folic acid on hemoglobin status of children aged 6-35 months, Rural Area, Tamilnadu, 2003: A double blind, randomized comparative trial'

By

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Dissertation project submitted in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology (M.A.E) of

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CERTIFICATION

This is to certify that this dissertation, entitled **'Effectiveness of iron alone and iron with folic acid in liquid form on the hemoglobin status of children aged 6 to 35 months, Rural area, Tamil Nadu, 2003: A double-blind, randomized comparative trial'**, submitted by Dr. S. Parvathy, in partial fulfillment of the requirements for the degree of Master of Applied Epidemiology, is the original work done by her and has not been submitted earlier, in part or whole, for any other (Publication or degree) purpose.

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DIRECTOR

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Abstract

Background

Iron deficiency anemia is a major public health problem among children below three years of age. The National Nutritional Anemia Prophylaxis Programme initiated the iron supplementation programme using the tablets in the year 1970. However, a high degree of non-compliance observed in this age group due to difficulty in swallowing the tablets posed a major problem to the success of the programme. The liquid iron supplementation for children which was introduced at a later stage was also withdrawn due to higher cost. This reinforced the need for use of an alternate iron preparation in this age group. In view of this, the present study was undertaken.

Objective

The main objective of the study was to compare the effectiveness of iron alone and iron with folic acid in liquid form on hemoglobin status of children aged 6 to 35 months in Thimmavaram village, Reddipalayam Primary Health Centre, Saidaepet Health Unit District, Tamilnadu, following administration of the supplement for 100 consecutive days.

Methodology

In this double blind, randomized, comparative trial, 106 children aged 6 to 35 months participated. They were supplemented with Iron III hydroxide Polymaltose Complex (IPC) either in the form of iron alone or iron with folic acid (IFA) for 100 days with a dose of 2 mg / day. Hemoglobin was assessed both in the baseline and at the end of the intervention. Compliance rate and the reasons for non-compliance were obtained.

Results

A significant increase in mean hemoglobin(g/dl) concentration was observed in both the intervention groups ($p<0.001$). However, the mean hemoglobin(g/dl) concentration change between the groups was not statistically significant ($p>0.05$).Good compliance (70 and more doses) of 76% and 63% was observed in the iron alone and IFA groups. Side effects (reported) like vomiting and diarrhoea were very few in both the groups.

Conclusions

Liquid IPC in the form of iron alone or iron with folic acid significantly improves the hemoglobin concentration of children aged 6 to 35 months. Compliance is good with this form of iron when compared to that of the tablets.

1. Introduction

Anemia is the reduction in the oxygen carrying capacity of blood due to reduced levels of hemoglobin concentration and red cell mass (Hematocrit) leading to tissue hypoxia. It reflects the disturbance of the dynamic balance between production and destruction of erythrocytes and hemoglobin. A child is said to be anemic when the hemoglobin and or Hematocrit is two standard deviations below the mean for that particular age and sex.

Despite considerable efforts to decrease the prevalence for the past 3 decades, iron deficiency continues to be the single leading nutrient deficiency in the world. The World Health Organization (WHO) estimates that about 2 billion people suffer from iron deficient anemia and 4 billion people have iron deficit[1-5]. Differences in the prevalence of anemia among the developing countries are wide with the poorest countries being most affected. The Fourth Report on the World Nutrition Situation, Geneva,2000[2] indicates that the South East Asian countries have the highest prevalence of iron deficiency anemia (39%) . The population groups most affected are pregnant women and children in both developed and developing countries[1-3]. The prevalence of anemia amongst pre- school children is 42 to 53% and 47 to 64% in Africa and South central and South East Asian regions respectively[1]. The intervention approaches that appear quite feasible in United States or Europe are impractical in resource poor countries like India[6].

As per the World Health Organization Report[3] (2000) 75% of the anemia is assumed to be due to iron deficiency and the prevalence of iron deficiency anemia (IDA) varies from <10% in industrialized countries to almost 40% in Southeast Asia . In India, several studies in various age groups of children using different methods of hemoglobin assessment, have reported the prevalence of anemia to be in the range of 45-85%[7-18].

2. Justification

2. 1. For The Study

The iron requirements of infants and children are particularly high due to rapid growth. In developing countries, about half the infants are anemic by one year of age[19]. An important factor contributing to this high level is maternal anemia which in turn might lead to reduced iron stores of the new born[20] . The United Nations Children's Fund (UNICEF)/ WHO Joint Committee on Health Policy (1994) called for implementing a preventive iron supplement programme for all infants and children where the prevalence of IDA among pregnant women is 30 percent or more. As per National Family Health Survey II[21], (1998-1999) the prevalence of anemia among all women of reproductive age (15-49 years) in India is 52%. In Tamilnadu, iron deficiency anemia among pregnant women is about 50%

Iron-deficiency anemia among children has been demonstrated to be associated with impaired cognitive performance[22,23], motor development, coordination, language development, scholastic achievement[24-28] and the most important irreversible brain dysfunction[29]. In terms of public health, the consequences of severe anemia with or without iron deficiency are increased child morbidity and mortality[30].

An expert consultation committee has also concluded that IDA impairs the mental and motor development and the behavior of infants[31]. The long-term developmental outcome of iron deficiency has been detected up to three years after the deficiency has been properly treated[32].

Several surveys report that in India, not only is supplementary feeding delayed more than 6 months but the type of supplementary foods given to infants also have low bio available iron. This implies that some form of iron supplement is needed by most infants between 6 months and 2 years of age[33]. *Furthermore, iron supplementation at a later age does not reverse the adverse effects of moderate to severe iron deficiency anemia that occured during the first 18 months of life* [31,34-36].

2. 2. For Use Of Liquid Iron Supplementation

The National Nutritional Anemia Prophylaxis Programme (NNAPP) later renamed as the National Nutritional Anemia Control Programme (NNACP) has been ongoing since early 1970. The program is yet to achieve its objective of reducing anemia prevalence in the targeted intervention group i.e children under five years. Reasons cited (Indian Council of Medical Research (ICMR) Evaluation, 1989) for this were (a) insufficient supply of the tablets, (b) low coverage of the target population and (c) difficulty in swallowing of the tablets by the children[37,38] . The report of the Task Force on Micronutrients, 1996 also states that the main limitations of the programme were poor compliance and irregular supplies. It was suggested that poor compliance can probably be overcome by use of a liquid iron supplementation as opposed to tablets particularly among children aged 6 to 35 months.

2. 3. For Use Of Iron III Hydroxide Polymaltose Complex

Iron III hydroxide Polymaltose Complex (IPC) is a novel iron preparation, which contains non-ionic ferric iron and polymaltose in a stable complex. Its non-ionic state helps in avoiding the gastro-intestinal irritation that is common with other forms of iron salts[39,40].

Iron absorption from IPC is a physiologically controlled active process unlike other ferrous salts where the absorption is by a passive process. In this process, apo - transferrin (a transferring molecule that does not contain iron) is found to take up the iron from IPC. It is then transferred to intestinal mucosa for further uptake by transferrin. Due to this, the accidental overloading of iron does not happen with the use of this particular form of iron unlike other ferrous salts[41,42].

Using a twin isotope technique (Fe^{55} and Fe^{59}), it has been observed that there is no difference in the absorption of the trivalent iron contained in the IPC and the bivalent iron in the ferrous sulphate[43-45]. So far, no known interaction of IPC with any food stuff or medications has occurred *in vivo* or *in vitro*[46].

Studies in children as such are very few and most of them are prevalence studies. To the best of the investigator's knowledge, only one comparative study by Schmidt B J [47] has reported study in children using liquid iron supplementation of Iron III hydroxide Polymaltose Complex and Ferrous sulphate. Moreover, it was found that in India, studies reporting the prevalence of folic acid deficiency anemia among children and the effectiveness of adding folic acid to routine iron supplementation are very few . Given this background, this study was undertaken to identify an iron supplementation that helps in higher compliance and offers effective rise in hemoglobin concentration in 100 days.

3. Goal

To identify a mode of iron supplementation to children below three years that ensures a high level of compliance and correction/ prevention of anemia.

4. Objectives

1. To estimate the change in the mean hemoglobin (g/dl) concentration in children aged 6m-35 months on administration of 20mg of iron alone or 20mg of iron and 140μg of folic acid in liquid form for a period of 100 consecutive days.

2. To estimate the compliance rate in these children.

3.To identify factors that affect compliance.

4. To propose appropriate recommendations for programme strategy re-design based on the results of the study.

5. Literature Review

5.1. Introduction

Anemia is a condition which is characterized by a reduction in red blood cell volume and a decrease in the concentration of hemoglobin in the blood. Commonly, anemia is the final outcome of a nutritional deficiency of iron, folic acid, vitamin B12 and some other nutrients. Although many other causes of anemia such as hemorrhage, infection, genetic disorders, and chronic disease have been identified, nutritional deficiency, due primarily to a lack of bioavailable dietary iron, accounts for the majority of cases of anemia[48-50].

5. 2. Historical Background Of Iron Deficiency Anemia

Ancient Greeks recognized the benefits of iron salts to improve muscular weakness among injured war veterans. The weakened sufferers hoped to regain strength by drinking water in which a sword had rusted[51]. In 16th century the term "chlorosis" was associated with a series of symptoms like pallor, fatigue, poor appetite, gastro intestinal, neurological, and menstrual disturbances common in adolescent girls[52]. In the 18th century, blood was shown to contain iron, and from 1832 to 1843, chlorosis was noted to be associated with low levels of iron in the blood and a reduced number of red cells[53]. Hemoglobin was discovered by Hoppe-Seylers in the 19th century. A method of estimating the hemoglobin concentration by color comparison to a standard was described by Gowers by about 1880. This was quickly followed by Sahli hemoglobinometer which is used even today with certain modifications. Understanding of anemia improved around 1890s when, Hufner, Haldane, and Smith demonstrated stoichiometric relationships between hemoglobin and its iron content, iron, and oxygen, and hemoglobin and oxygen carrying capacity[54].

5. 3. Epidemiology Of Iron Deficiency Anemia

5.3. 1. Global

The importance of anemia was recognized by the World Health Organization (WHO) as early as the first meeting of Joint Advisory Committee in 1949. A national survey of anemia was sponsored by WHO in Mauritius between 1955 and 1958. The prevalence

of hypo chromic microcytic anemia ranged between 15 to 64%. This anemia subsequently responded to bread enriched with iron. Follow up investigations of nutritional anemia among pregnant women in India revealed that 38% of them were anemic; half of them with severe anemia who responded to combined iron and folic acid supplementation.

The WHO first attempted to collate the available information about women from a global perspective in 1982[55]. The same was updated in 1992[56]. The prevalence was highest in young children and pregnant women, and varied from about 56% in young children in Africa and South Asia, and 20 to 26% in Latin America and East Asia, to about 8 to 18% in developed countries. This did not include the large group of individuals who were iron deficient but without anemia[56]. In the U.S. and Europe, the prevalence of anemia is 7 to 12 percent among women and children The WHO estimates (2000) indicate 2 billion people to be anemic globally and 4 billion to be iron deficient[2,3] which is due to the fact that iron deficiency anemia generally occurs after iron stores have been depleted.

Table 1. Global Prevalence of Anemia and Iron Deficiency

Region	Anemia		Iron Deficiency Anemia*		Iron Deficiency†	
	Number	%	Million	%	Million	%
Africa	237	39	175	29	438	73
Americas	142	18	106	14	266	34
SEA	765	53	574	39	1435	99
Europe	80	9	60	7	150	17
E.Med.	179	38	135	29	337	72
W.Pacific	578	38	434	29	1084	72
TOTAL	1981	34	1484	26	3710	64

Source : Malnutrition, The Global Picture, World Health Organization, Geneva,2000

* Assuming that 75% of the anemic population is also iron deficient.

† Estimated as 2.5 times the prevalence of iron deficiency anemia in regions with up to 40% prevalence of iron deficiency anemia. When prevalence is >40%, virtually the entire population is iron deficient.

5. 3. 2. Developing Countries

According to World Health Organization (2000), 35 percent of women and 43 percent of young children in the world are anemic globally. In developing countries however, about 50 percent of women and young children are anemic[2,3]. Wide inter country differences in the prevalence of anemia are observed among developing countries with poorer countries being most affected (Table 1) . The prevalence among pregnant women in East Central Africa, West Central Africa, Southeast Asia and South Central Asia is 47, 56, 63 and 75% respectively. Among pre-school children, also in these areas, the prevalence is high: 42 to 53% in Africa and 47 to 64% in South Central and South East Asia respectively. Studies report that anemia is highly prevalent in Kazakhstan, Uzbekistan and other countries of former Soviet Union. The highest overall rates of anemia are reported in Southern Asia and certain regions of Africa[4]. About 50% of global anemic women live in the Indian sub continent where about 88% of pregnant women are affected[37].

5. 3. 3. India

Micronutrient deficiencies like Vitamin A, Iron and Iodine deficiencies are widely prevalent in India and this is attributed more to the improper, inadequate intake rather than non-availability.

Several surveys, during the last four decades conducted in different parts of India, though admittedly of varying quality in terms of methodology, age coverage and hemoglobin cut offs used, indicate that iron deficiency anemia among infants and toddlers vary from about 40% to 86% (Table 2).

Table 2 : Prevalence of iron deficiency anemia among infants and toddlers in India

Study Region /Reference	Age	Prevalence [%]	Criteria For Assessment*
North India			
Delhi	6m –3 y	60	Hb <12g/dl
Dhar et al, 1969[7]			
ICMR,1977[8]	1 –3 Y	83	Hb <10.8g/dl
Gomber al,1998[14]	3m –3y	76	Based on response
Kapur et al,2002[13]	9 –36 m	64	Hb <11g/dl
Ludhiana			
Uberoi et al, 1972[9]	<3y	70	Hb <11g/dl
Varanasi			
Singla et al,1982[15]	6m- 5y	Urban 56; Rural 75.6	Based on response
Agarwal et al,1986[10]	3 m- 3y	55	Hb <11g/dl
South India			
Vellore, ICMR, 1977	1 –3 y	54.3	Hb <10.8g/dl
Hyderabad ICMR,1977[8]	1 –3 y	60.5	Hb <10.8g/dl
	5 –6 m	63.3	
	7 – 9 m	77.5	
Raman et al,1990[11]&1992[12]	10 – 12 m	86.2	
	13 – 15 m	75.0	Hb <11 g/ dl
	16 – 18 m	75.0	
	19 – 24 m	76.9	
	24 – 36 m	47-57	
West India			
Mumbai, ICMR,1977[8]	1 – 3 Y	70.6	Hb 10.8g/dl
Pune, ICMR,1977	1 –3 Y	79	Hb <10.8g/dl
Malin et al, 1982[18]	1-3 y	61	PCV<33%
East India			
Kolkatta			
ICMR,1977	1-3 Y	38.9	Hb <10.8g/dl
India combined data	0-3Y	65	Hb <10.8g/dl

* Hemoglobin estimation and based on response to supplementation

The highest prevalence of anemia was found in Delhi (83%) followed by Pune (78%), Mumbai (70.6%), Hyderabad (60.5%), Vellore (54.3%) and Kolkatta (38.9%). Prevalence of severe anemia was 36% in Delhi and about 14% in Hyderabad and Pune[8] Earlier studies from different regions in the country during the last three decades have also reported a similar high prevalence[12,14,15,57,58].

5. 3. 3.1. North India

In an Integrated Child Development Scheme (ICDS) centre of an urban slum of Delhi, the prevalence of anemia was 64% in children aged 9-36 months[13]. In a rural setting of Ludhiana, Punjab, 70% of children in the below three years were anemic[9]. In a Varanasi study[10] (1986), 55% of children aged 3 months to 3 years were found to be anemic and off springs of anemic mothers had a significant higher prevalence of anemia. Singla et al[15] (1982) reported that prevalence rates in urban and rural pre school children(6 months to 5 years) of Varanasi was 56.2 and 75.6% respectively. In 2002, Kapur et al[13] observed that 64% of children aged 9 to 36 months were anemic and 7.8% of them were severely anemic.

5. 3. 3. 2. South India

The ICMR, Hyderabad study in 1977[8] reported the prevalence of IDA among children below 3 years of age as 63% using a hemoglobin concentration of 10.8g/dl as the cut-off to define anemia. In a multi centric study by Food and Nutrition Board & UNICEF in 1981 [59], the prevalence of anemia in urban centres of Madras (currently Chennai) and in villages near Hyderabad was 19.1% and 66.3%. Visweswara Rao[60] reported that studies from Hyderabad in 1978, 1980 and 1983 indicated that the prevalence among children aged 1 to 6 years was around 50 to 70%. A study by NIN Hyderabad (1992), reported that children between 1-3 years were the most affected by IDA. The prevalence of IDA was found to be 63% among children 12-23 months old, 67% among those 24-35 months old and between 27-44% in 3-5 years old age group.

5. 3. 3. 3. West India

Malin et al[18] (1988) reports an overall anemia prevalence of 43% in a slum area of Pune in children aged 6 to 60 months. The children aged 12 to 36 months were the most affected and accounted for 61% of the total prevalence. Studies from Gujarat[61] report a prevalence of 66% in children aged 1 to 5 years. Seshadri[57] reported that studies carried out between 1980 and 1996 in Baroda have indicated a prevalence of 67% among urban pre school children.

5. 3. 3. 4. East India

The multi centric study done by Government of India[59], reported the highest prevalence of anemia (96.3%) among children aged 1 to 5 years in villages near Kolkatta. The same study reported that prevalence of severe anemia was also highest in Kolkatta (18%)

The National Family Health Survey[21] (NFHS II) conducted in 1998-99 reported the prevalence of iron deficiency anemia in children aged 6 to 35 months to be 74% in India and 69% in Tamilnadu (Table 3). The anemia level was highest in the 12-23 months age group (77.7%) as compared to the children in the age group of 6-11 months (71.7%) and 24-35 months (72%). Earlier studies from different regions in the country during the last three decades have also reported a similar high prevalence[12,14,15,57,58].

Table 3 : Percentage of children age 6-35 months classified as having iron-deficiency anemia by state, India, 1998-99 (NFHS II)

State	Percentage of children with Anemia			
	Total	Mild	Moderate	Severe
India	74.3	22.9	45.9	5.4
North				
Delhi	69	22.2	42.9	3.9
Haryana	83.9	18.0	58.8	7.1
Himachal Pradesh	69.9	28.7	39.0	2.2
Jammu &Kashmir	71.1	29.1	38.5	3.5
Punjab	80.0	17.4	56.7	5.9
Rajasthan	82.3	20.1	52.7	9.5
Central				
Madhya Pradesh	75.0	22.0	48.1	4.9
Uttar Pradesh	73.9	19.4	47.8	6.7
East				
Bihar	81.3	26.9	50.3	4.1
Orissa	72.3	26.2	43.2	2.9
West Bengal	78.3	26.9	46.3	5.2
North east				
Arunachal Pradesh	54.5	29.1	24.7	0.7
Assam	63.2	31.0	32.2	0.0
Manipur	45.2	22.6	21.7	0.9
Meghalaya	67.6	23.4	39.8	4.3
Mizoram	57.2	32.2	22.7	2.3
Nagaland	43.7	22.0	18.7	3.0
Sikkim	76.5	28.4	40.7	7.5
West				
Goa	53.4	23.5	27.9	2.0
Gujarat	46.4	29.5	14.4	2.5
Maharashtra	76.0	24.1	47.4	4.4
South				
Andhra Pradesh	72.3	23.0	44.9	4.4
Karnataka	70.6	19.6	43.3	7.6
Kerala	43.9	24.4	18.9	0.5
Tamilnadu	69.0	21.9	40.2	6.9

5. 3. 4. Iron deficiency anemia in infants and children

5. 3. 4. 1. Iron balance in children

5. 3. 4. 1. 1. First six months of life

During the first four months of life, the total body iron content is fairly adequate due to the trans placental transfer of storage iron content[32,62] and about half the storage iron is mobilized for the production of hemoglobin, myoglobin and enzymes. About fifty percent of the iron in breast milk is absorbed compared with about fourteen percent of the iron in other milks or breast milk substitutes[32]. Hence, healthy term infants are unlikely to become iron deficient in the first six months[63-65]. However, infants who are pre-term or who have low birth weight[66] or those who are born to anemic mothers have poor iron stores [67,68] could manifest with iron deficiency in the first three to six months of life itself.

5. 3. 4. 1. 2. Six to twelve months of life

After about 4- 6 months, infants need more iron than can be supplied in breast milk alone. In industrialized countries, this problem is tackled by fortification of supplementary foods recommended for all infants starting at around 6 months. In developing countries, about half the infants are anemic by one year of age[19].

In India, not only is supplementary feeding delayed beyond 6 months but also the type of supplementary foods given to infants contains low bio available iron. This implies that some form of iron supplement is needed by most infants between 6 months and 2 years of age[33]. After 2 years of age , the prevalence of anemia tends to fall because iron requirements are lower and children start to eat a varied diet[36] . However, the high prevalence in many countries persists due to (a) iron depletion in early years, (b) inadequate diet [69] and (c) frequent parasitic infestations in children.

5. 3. 4. 1. 3. Other risk factors for iron deficiency anemia

Low birth weight (LBW), which is especially common in developing countries is clearly a risk factor for anemia early in infancy. Infants with LBW are born with

reduced iron stores which are depleted by 2 to 3 months of age. The International recommendation for LBW infants is to start supplemental iron in the form of drops as early as 3 months of age[4].

Premature clamping of the umbilical cord deprives infants of up to one third of their potential blood volume which in turn leads to reduced iron resources. The delay in clamping until one minute after the cord ceases to pulsate, and holding the infant at or below the level of the placenta can significantly improve the amount of blood and therefore the amount of iron delivered to the new born infants[70].

5. 3. 4. 2. Public health importance of iron deficiency anemia in infants and children

Infants and preschool children form the most vulnerable group as they have increased risk of iron deficiency and anemia due to high physiological demands combined with low iron stores, inadequate dietary intake of bio available iron, and losses due to infection[48]. Iron deficiency is more widespread than iron deficiency anemia. For every person who is anemic, there is likely to be another person who is iron deficient, but not anemic. *In other words, if the prevalence of anemia is fifty percent or more, the entire target population is likely to be iron deficient and in need of an iron intervention*[1].

Infants who are fed canned, powdered, or fresh milks are at risk for iron deficiency at a younger age than infants who are exclusively breastfed. Introduction of iron-rich supplementary foods beyond six months makes the infant at risk of developing iron deficiency. Where iron-fortified complementary foods are not widely and regularly consumed by young children, routine iron supplementation is recommended beginning at six months[34].

5. 3. 4. 3. Functional consequences of anemia

Anemia leads to a reduction in the transport of oxygen to the cells of the body. The main signs and symptoms of anemia are lethargy, fatigue, shortness of breath, and pallor of the skin and inner eyelid. When anemia is moderate to severe, the nail beds of

the fingers, the palms, and the inside of the eyelids become pale". As anemia becomes more severe, anemic individuals may experience palpitations of the heart and heart failure.

Iron-deficiency anemia among children has been demonstrated to be associated with impaired cognitive performance[22,23] motor development, coordination, language development and scholastic achievement[24-28]. In terms of public health, the consequences of severe anemia with or without iron deficiency are increased maternal and child mortality[30]. A significant body of evidence also points to iron deficiency anemia (tissue iron deficiency) leading to impaired productivity and delayed child development. More evidence is needed in support of the suspected relationships between iron deficiency anemia and low birth weight and between iron deficiency anemia and infectious disease.

Infants with iron deficiency anemia have been shown to experience delays in mental development compared to infants who are not anemic[23] . Iron deficiency also affects the emotional state of infants, making them more cautious and maintaining closer contact with their mothers [71,72]. These infants may interact to a lesser degree with their environment, and the lack of interaction could impede their ability to learn.

Because most brain development after birth occurs during the first two years of life, infants and children younger than two years old are at higher risk of developmental delays than older children. Delays among children younger than two years old includes both mental and motor development and these are not fully reversed after the children were treated with iron[73].

The relationship of iron status, immunity and infections in children is yet unclear. Some studies have demonstrated impaired cell immunity due to iron deficiency anemia[74,75] whereas some did not show any effect[76] .

5. 4. Preventive Strategies To Control Anemia

The three basic approaches for prevention of Iron deficiency anemia are:

a) Supplementation with medicinal iron

b) Dietary modifications which includes food fortification and enrichment

c) The control of infection

Although the technology for the fortification of salt has been available for the past one decade, it has not been introduced on a large scale to combat iron deficiency anemia in India, despite being strongly recommended[53]. Iron-fortified salt is currently being produced on a small scale only by a few private manufacturers and by the Food and Nutrition Board of the Ministry of Food and Agriculture. Large-scale introduction of iron-fortified salt is currently being organized only in Tamilnadu by the Tamilnadu Government with support from UNICEF, The Food and Nutrition Board and the Tamilnadu State Industrial Corporation.

In view of this, a new technology for the double fortification of salt with iron and iodine has been recently developed[54] and this is currently undergoing field evaluation. If the iron balance in the total population is improved through iron-fortified salt, the anemia control programme among pregnant women and children will have better success. Iron fortification of salt is being suggested as an adjunct and not as an alternative to the present anemia control programme.

5. 4. 1. Supplementation with medicinal iron

Supplementation with medicinal iron has the advantage of producing rapid improvements in iron status. As a strategy it also has a desirable specificity. It can be targeted at the population groups at the greatest risk of becoming iron deficient i.e infants, preschool children and pregnant women.

Intervention trials conducted in children below three are few. In a study of Honduras and Swedish infants aged 4-9 months, the effect of iron supplements at the level of 1mg per kg body weight per day was investigated[77]. The Honduran infants who received iron from 6 month onwards showed a significant drop in the prevalence in anemia. A similar reduction among Swedish infants was not observed. The reason as given by the author was that the prevalence of anemia among these infants was low to begin with.

However, the iron supplementation from 4 month onwards produced a significant rise in hemoglobin among both groups of Honduran and the Swedish infants.

A meta analysis of weekly vs. daily supplementation refers to four trials in young children, of which only one was in children 6 to 24 months[78]. The dose level of iron was 8 mg given along with zinc and retinol daily for 12 weeks. Reduction of anemia was very substantial, from the initial 50.9% to final 5.7%. These limited studies indicate that the dose level 1-2 mg/kg body weight that is equivalent to 10-20 mg iron can produce the desired results.

5. 4. 2. Iron dose for prevention of anemia

A single safe dose that is effective for all children under 2 years old that can be easily dispensed by non-literate mother is required[16]. Usually iron drops (or syrup) are given in two to three times daily doses schedule. Recently, use of single daily dose of iron drops has been found to be equally efficacious as three times daily doses, (at the same total iron dose on treatment of anemia) without side effects[79].

In a prophylactic programme, a supplementation of 1-2 mg iron/kg/day is adequate for prevention of iron deficiency anemia. A dose of 2 mg /kg/d could be considered in India as nearly one third babies born have low birth weight[21]. However, for implementing community based anemia prevention/control programme calculation of iron dose in terms of body weight is impractical. A simple and suitable fixed dose strategy rather than an exact dose based on a body weight basis is more appropriate.

5. 4. 3. Fixed dose strategy

The International Nutritional Anemia Consultative Group (INACG), based on a iron dose of 2 mg/ kg body weight for prevention of anemia, have recommended an uniform dose of 12.5 mg for children aged 6-24 months[34]. This is based on the assumption of 5 percent iron absorption, which is a very conservative estimate of absorption[17]. A 12.5-mg oral dose of iron would provide 0.625 mg of absorbed iron. The 12.5 mg dose is equivalent to 2.5 mg /kg body weight for a 6-month-old child with an average weight of 5 kg, 1.6 mg/kg body weight for a 12-month-old infant weighing 8 kg, and 1.2 mg/kg

body weight for an 18-month-old infant weighing 12 kg. The total iron requirement remains at 0.7 mg per day for infants up to 18 months of age[80] and is not dependent on body weight; thus, the 12.5 mg dose would also meet almost 90 percent (assuming absorption 5% X 12.5= 0.625; 0.625/0.7 X 100= 89%) of the estimated total iron requirement of children 6 to 18 months old. Where iron absorption is higher because of low iron stores, the upper safe limit of intake would not be exceeded with this dose.

5. 4. 4. Folic acid supplementation along with iron supplement

Though folic acid has been used in the National Nutritional Anemia Control Programme for years together, the role of folic acid in reduction of anemia has been controversial. In India, studies reporting the prevalence of folic acid deficiency anemia among children are very few.

Gomber et al[14] reports that 5% of children of an urban slum were folic acid deficient. Low birth weight and pre term babies could be at risk of folic acid deficiency due to rapid growth and would need supplementation of folic acid[81]. Hence, it seems that the main rationale for including folic acid in iron supplements for anemic pregnant women and children is to reduce the risk of neural tube defects in off springs and prevent folic acid deficiency and megaloblastic anemia in the first 2 months of life[82].

A meta-analysis of 22 studies in which non-anemic pregnant women had been supplemented with folic acid for at least 16 weeks, with or without iron was conducted[83]. Nearly 50% of the studies in the meta-analysis were conducted in the U.K. over 30 years ago. Only four were conducted in the last 20 years. The most significant effects were seen in Africa, where folic acid deficiency and megaloblastosis may have been caused by malaria. Premature, low birth weight infants treated with iron, vitamin E, and folic acid showed an improvement in hemoglobin concentrations when they were also given parenteral vitamin B12[82]. Folic acid treatment was associated with a 40% reduction in risk of anemia in late pregnancy and a 35% reduction in risk of megaloblastosis.

A WHO collaborative study in Burma and Thailand found no incremental benefit of folate on the hemoglobin concentrations of pregnant women or non pregnant women [84] but these countries are not known to have a high prevalence of deficiency.

Small non significant increase in Hemoglobin-usually compared to iron alone have been reported in pregnant women in Australia[85], Burma[86], India[87,88], Liberia[89], Nigeria[90] and Thailand[91] .

A significant increase in hemoglobin was found only in South Africa[50] and in a British study in which addition of folic acid to iron supplements improved hemoglobin of low birth weight infants aged 6 to 9 months compared to iron alone supplements[81] .

5. 4. 5. Forms and types of iron salts

Liquid iron preparations contain iron salts/complexes like ferrous sulphate, ferrous fumarate, ferrous gluconate, ferric ammonium citrate, colloidal iron and ferric hydroxide polymaltose complex (Iron Polymaltose Complex or IPC). Elemental iron content in these salt/complexes is variable[58] .The absorption of elemental iron depends on the particle size. EDTA has the advantage of greater stability than ferrous iron, good absorption and improves the absorption of non-heme in the diet. Its only drawback is the higher cost. Amongst ferrous salts, ferrous fumarate has a low ionization constant and high solubility in the entire pH range of the gastrointestinal tract. It does not (a) precipitate proteins or have the astringency of ionizable forms of iron and (b) interfere with proteolytic or diastatic activities of the digestive system. Ferrous fumarate is the least toxic of the three popular iron salts.

5. 4. 5. 1. Iron (III) Hydroxide Polymaltose Complex (IPC)

Iron III hydroxide Polymaltose Complex has non-ionic ferric iron and polymaltose in a stable complex. Iron absorption from IPC is physiologically controlled and it is by an active process, where apotransferrin (a transferring molecule that does not contain iron) is found to take up the iron from IPC. It is then transferred to intestinal mucosa for further uptake by transferrin[41]. The quantity of this carrier protein depends on the iron stores of the body. This makes the iron absorption from IPC to be rapid in anemic

condition and absorption will slow down or halt when the iron store reaches the optimum level. Hence there will be no overloading of iron with the use of IPC unlike other ferrous salts where iron absorption is passive and concentration gradient dependent.

Bioavailablility is found to be similar, particularly between ferrous sulphate, ferrous fumarate and IPC[43] . Rise in hemoglobin following supplementation of ferrous salts and IPC were also found to be similar[92,93] whereas one study conducted by Jacobs P[39] reported better tolerance to IPC. Other advantages of iron polymaltose complex is that it does not produce free radicals as opposed to conventional iron salts[94]. Its non-ionic state helps in avoiding the gastro-intestinal irritation that is common with iron salts[39,40]. IPC also do not stain the teeth and high elemental content of iron facilitates once a day dosing. Thus IPC may have a potential role in longer term supplementation programme[39] A joint OMNI/USAID/UNICEF consultation has recommended that the most practical iron supplement for use in infants and young children is an aqueous solution of a soluble ferrous salt, such as ferrous sulphate or a ferric complex, such as iron polymaltose.

5. 5. Cost Effectiveness

Under NNACP programme, IFA liquid formulation was discontinued in view of not being cost effective (Cost being Rs. 5.98 per beneficiary as compared to Rs.0.49 for tab per beneficiary), and problems encountered in procurement and distribution of liquid preparations[95] .

5. 6. Summary

Iron supplementation should be given to "high risk target groups" eg. Children aged 6-35 months.

A. Factors that necessitate iron supplementation in children aged 6-35 months are high physiological requirement, low intake of iron rich foods, low bioavailability of iron, public health benefit due to intervention.

B. Factors that warrant usage of liquid form are poor compliance when tablets are given (due to taste preference and inability to swallow in young children)

C. Factors that favour supplementation of Iron (III) hydroxide Polymaltose complex are equal efficacy as that of the conventionally used ferrous salts, high compliance due to the addition of polymaltose component, very few side effects when compared to the conventional salts and the most important of all being the absence of accidental overloading .

In view of all the issues discussed above, this present study aims to find the solutions to address the problems in children possibly by reintroduction of liquid preparation of iron.

6. Methodology

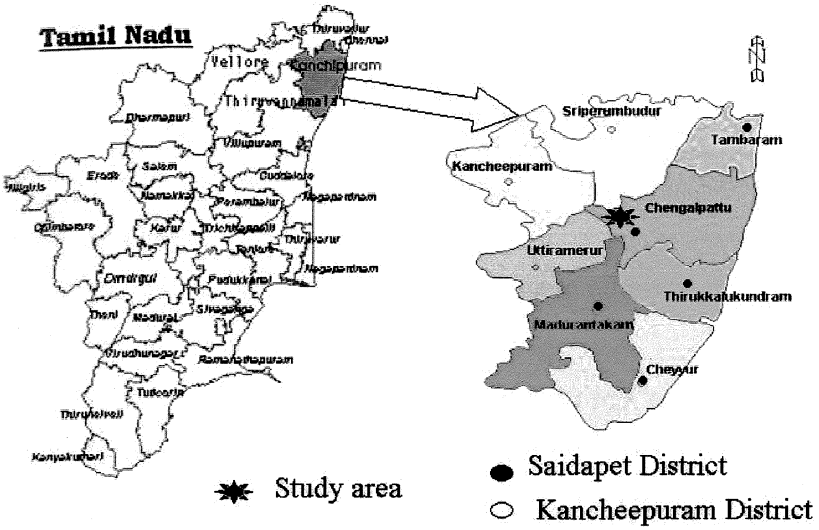
6. 1. Study Area

The Kancheepuram revenue district is one of the thirty districts of the state of Tamilnadu. This is further divided into two Health Unit Districts for administrative reasons i.e Kancheepuram Health Unit District and Saidapet Health Unit District. The Saidapet HUD has six blocks and twenty three Primary Health Centres. The study was conducted in Thimmavaram Health Sub Centre, Reddipalayam Primary Health Centre, Saidapet Health Unit District (HUD).The selected sub centre is about 62 km away from Chennai city. The total population of the selected HSC is 5035 and children aged 6 to 35 months were 257.

6. 2. Sampling design

All the primary health centres were listed and one was selected (Reddipalayam) by simple random method. One Health Sub Centre (HSC) (Thimmavaram HSC) of this PHC was selected by simple random method again. There are four villages in this HSC. Two villages (Thimmavaram and Choolaimedu) were selected for study purposes by population proportion to size method. The total children in the age group of 6 to 35 months in these two villages were 145.

Map showing the location of study area



6. 3. Study design

Double blind, Randomized Comparative Trial

6. 4. Study Subjects

6. 4. 1. Inclusion Criteria

All children aged 6 to 35 months residing in the two selected villages and who are willing to participate in the study.

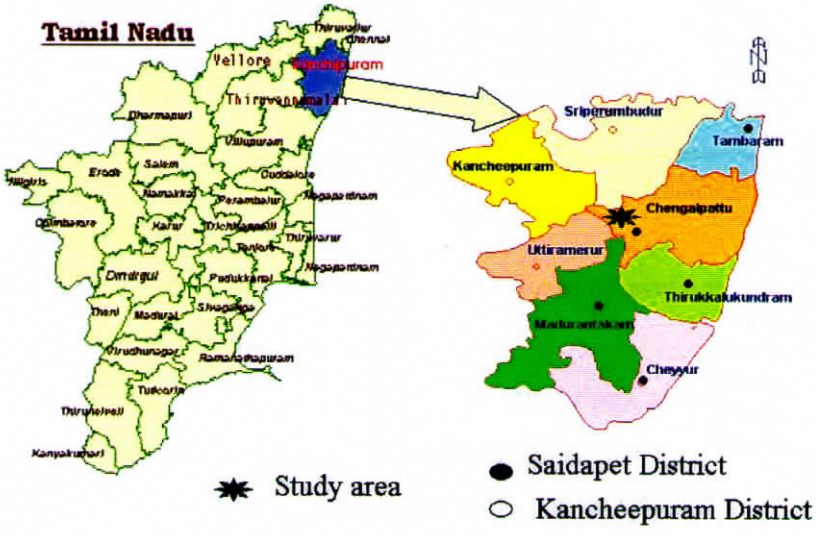
6. 4. 2. Exclusion Criteria

Children who were severely anemic (<7g/dl) and/or severely ill were excluded from the study since they would need therapeutic and special medical attention. However, for ethical reasons, they were referred to the primary health centre for therapeutic treatment.

6. 5. Anemia Definitions

(a) As per the WHO criteria (1989) for diagnosis of Anemia, the study subjects were divided into two groups based on hemoglobin concentration levels mainly into: anemic (<11 g/dl) and (b) non-anemic (11 &>11g/dl)

Map showing the location of study area



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Anemia was further graded as follows:

Anemia grading	Hemoglobin level (g/dl)
Mild	10 to 10.9
Moderate	7 to 9.9
Severe	Less than 7

6. 6. Intervention

Two types of liquid iron supplementations were administered to each child included in the study for 100 consecutive days :

a. 20 mg of Iron III hydroxide Polymaltose Complex (Mumfer® manufactured by Gopaldas Visram & Co. Navi Mumbai, India)

b. 20 mg of Iron III hydroxide Polymaltose Complex with 140 μg of folic acid (Vitcofol.com manufactured by FDC Limited, Thane, India).

Administration of Supplementation

Based on the random allocation method, each study participant was given one supplementation bottle which contained 75 doses (150 ml). One dose (2 ml) is equivalent to 20 mg of iron or 20 mg of iron with 140μcg of folic acid as the case may be. Each parent/guardian was supplied with a 2ml measuring spoon for them to administer the supplement to their respective children/ ward on a once a day basis.On completion of one bottle, the mother/ guardian of the participating child received one more bottle to complete the total 100 doses.

A fixed dose strategy of 12.5 mg/day of iron has been recommended by INACG for children aged 6 to 24 months[34]. However, it was observed that under the National Nutritional Anemia Control Programme (NNACP), children under five years receive 20mg of iron and 100μg of folic acid in tablet forms on a daily basis. Hence, in this study, a dose of 20 mg/day of iron (iron alone) or 20 mg/day of iron with 140 μg / day of folic acid was administered since all the commercially available preparations have a higher dosage than the required folic acid content of 100μg. As folic acid is water soluble and any excess is excreted in the urine, there is no possibility of over dosage of folic acid with this administration.

Compliance Card

Each parent/guardian was given a compliance card (Appendix 7) so as to enable them to make a 'tick mark' on every day of administration of the supplement.

6. 7. The Outcome Measure

The primary end point with respect to the effectiveness of the supplementation was an increase in 1g/dl of mean hemoglobin concentration in the study subjects of both intervention groups.

6. 8. Sample Size

To have a 95% chance of detecting as significant (at one sided 5% level) a 1g/dl increase of mean hemoglobin concentration , an assumption of standard deviation (of a single measurement of hemoglobin in both the groups) of 1.2, correlation factor of 0.3 and equal number in both the arms was made based on literature reviews. The needed sample size in each intervention group was 34.

$Z_{1-\beta}$ [one sided] =1.64 at α =0.05

With power 90%

$$n = \frac{2(Z_\alpha + Z_\beta)^2 \sigma^2_d}{(\mu_{dc} - \mu_{dt})}$$

where,

μ_{dc} = true value of difference in the outcome measure at 100 days and baseline for the control intervention

μ_{dt} = corresponding value for the test intervention

$\sigma^2_d = 2(1-\rho)\sigma^2$

σ^2 = variance of the outcome measure on a single individual

ρ = correlation coefficient between baseline and follow up outcome measures on a single individual

$$n = \frac{2[1.2^2 + 1.2^2 - 2 \times 0.3 \times 1.2 \times 1.2][1.64+1.28]^2}{1} = 34$$

Allowing for 20% dropout/refusals, the sample size required was calculated to be 40 in each intervention group.

6. 9. Randomization

6. 9. 1. Randomization – Sequence generation

All the study participants had equal opportunity to participate in the study. Randomization was done by the faculty, National Institute of Epidemiology, Chennai using the tables of random permutations (Source: Table 2, Moses & Oxford) .

6. 9. 2. Randomization – Concealment

The random treatment allocation made by the faculty, NIE was issued to the principal investigator in sealed envelopes.

6. 9. 3. Randomization implementation

The random treatment allocation sealed and supplied in envelopes was opened by the principal investigator only at the time of administration of the intervention.

The whole procedure was written and sealed in an envelope and was entrusted with the Director, National Institute of Epidemiology (NIE), Chennai. At no time was the faculty member responsible for randomization was in contact with the study children or the field investigators.

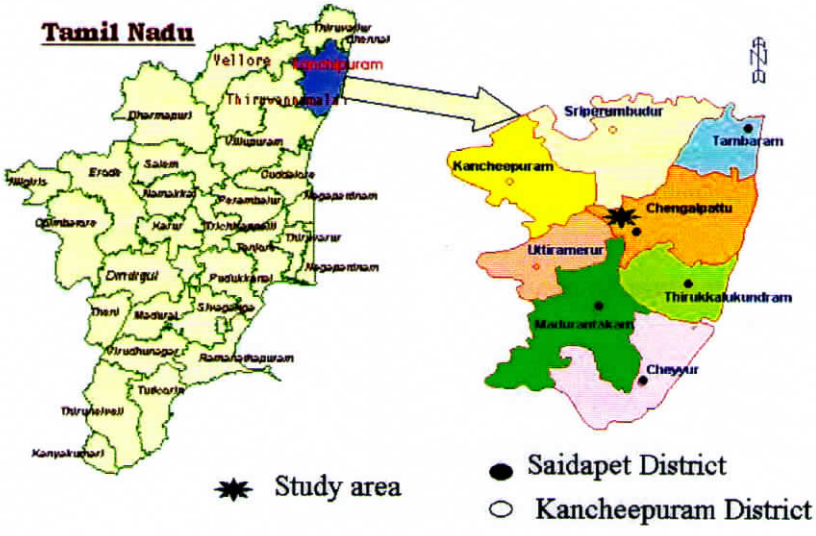
6. 10. Random allocation of the supplement

All the eligible children were assigned to the iron alone or iron with folic acid group. They remained in the same allocation group throughout the study period. Once the first eligible child was identified and contacted, the sealed envelope with the serial number "1" was broken and the specified allocation was administered to that child. The same procedure was then followed for every eligible child whose parent/ guardian gave written informed consent for participating in the study.

6. 11. Blinding

All the team members including the principal investigator and the participants were blinded to intervention assignment for the duration of the study. This was possible as

Map showing the location of study area



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them to their respective children / ward and recording of the same in the compliance card provided to them.

6. 15. Ethical Issues

The National Institute of Epidemiology (NIE) Institutional Ethics Committee Clearance was obtained for the conduct of the study. The informed written consent form (Appendix 1) was provided to all the parents/ guardians of the eligible children. The consent form had two parts viz.,the information sheet and the written consent form. The information sheet provided details regarding the purpose of the study, proposed interventions to be used, their benefits and expected side effects. It also explicitly stated that the participation of their children / ward is voluntary and they were free to withdraw from the study at any time. It clearly provided the name and the contact address of the principal investigator and the local village health nurse who was to be contacted for any additional information/ dissatisfaction.

Mother of a child giving her written consent for her child's participation in the study

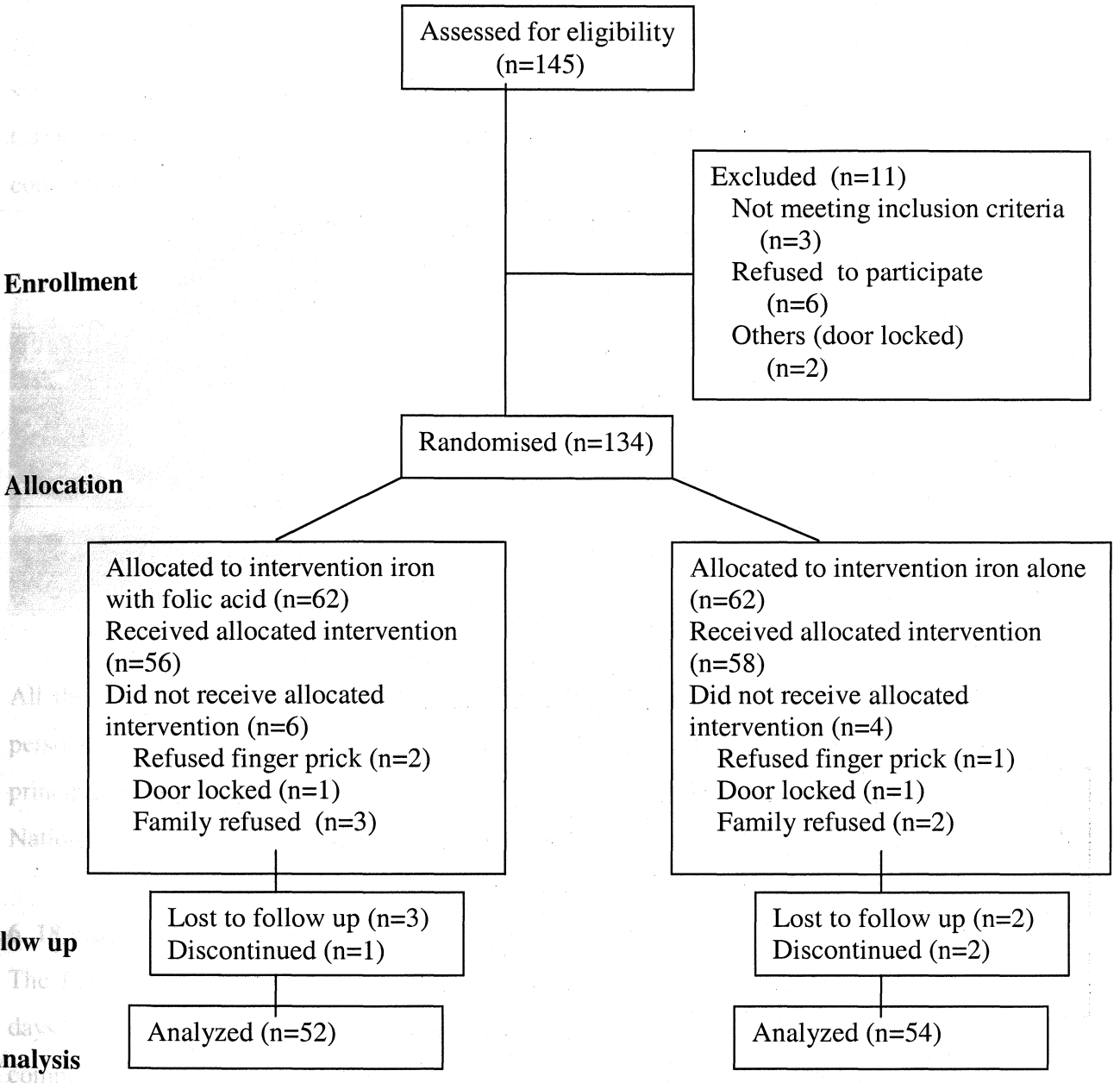
Informed written consent was obtained from all the parents/guardians for the willingness of their respective children/ wards to participate in the study. In the case of illiterates, the consent was obtained by means of left hand thumb impression in the presence of a local educated resident. The study was expected to benefit all the children who participated in this study. Those children who were severely anemic or ill were also taken care of by appropriate treatment administration or referring to the primary health care centre.

6. 16. Baseline Data Collection

The under three population of the two selected villages was 135 . All these children were screened at the baseline and the details were recorded (Appendix 4). Details regarding identification, socio economic status and general information, birth details were recorded in the pre tested questionnaire (Appendix 3) as per the responses of the mother/informant by trained field investigators. Maternal and child health register and immunization cards were verified for birth weight and immunization details in addition to the responses obtained from the parent/guardian. General examination of the children was done for presence of any severe illness. Anthropometric measurements like height and weight were recorded.

Screening of the children

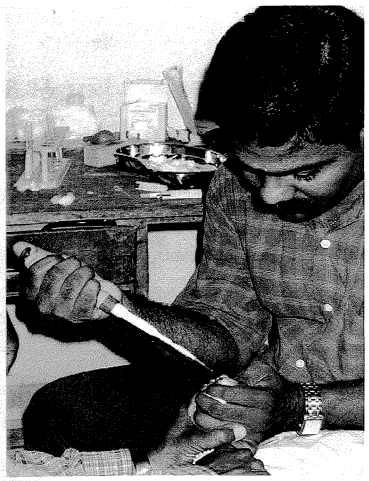
Flow Of Study Subjects



6. 17. Hemoglobin Estimation

Hemoglobin estimation for the study participants was done at baseline and at the end of intervention for 100 consecutive days. The trained laboratory personnel used the Cyanmethemoglobin method. The method is as follows:

Blood sample (20µl) was collected in 20µl Fin Pipette from the study subjects by using finger prick method. This was done in the left middle finger or big toe for infants. The sample was then added to 5ml of standardized Drabkins solution in a sample collection container which was inverted several times to mix the solution well. It was allowed to stand for 10 minutes. This solution was then transferred into the cuvete and read in a Calorimeter at 540nm.The values of hemoglobin were calculated against a standard concentration curve.



All the observations were made and recorded (Appendix 2)by the same laboratory personnel thus avoiding inter-observer bias. Every 5th sample was checked by the principal investigator for precision of the estimate and every 10th sample was sent to National Institute of Nutrition, Hyderabad for accuracy.

6. 18. Supervision And Monitoring

The field investigators and the principal investigator visited each child once in five days and once in 10 days respectively for the entire study period to check for compliance with respect to the administration of the intervention, reasons for non compliance and to gather information regarding any side effects.

6. 18. 1. Compliance Check

During each visit, the entries made in the compliance cards were checked. Enquiries regarding any side effects was made and the reported responses were noted down (Appendix 6). Care was taken not to enquire the mother with probing questions. If non compliance was observed in the last five days of each visit, then reasons for non-compliance were also noted down.

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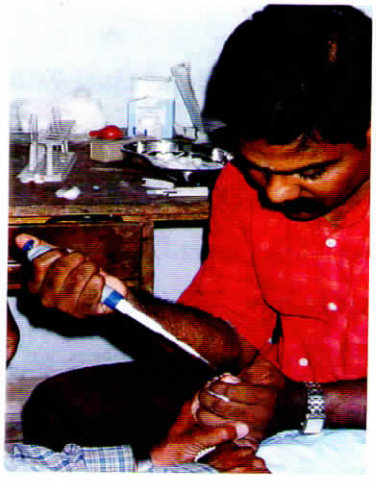

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6. 18. 2. Supplementation in take check

Cross checking of the total doses administered were checked by means of measuring the remaining supplement. However, this could not be a real estimate as this did not account for spillage or wanton wastage. One indirect method adopted was enquiring about the passage of dark stools by the child. As the mothers/ guardians were already briefed about the possibility of the child passing dark stools on administration of the supplement, this did not cause any alarm in the mother/guardian

6.19.DataAnalysis:

The Epi-info Version 6.04, ISTAT Vesion 2.0 (Institute for research in Medical Statistics, Chennai) has been used for analysis. The analysis has been done in the two groups: children who received iron alone and those who received iron with folic acid. The prevalence of iron deficiency anemia has been expressed as the percentage of children below the cut off of less than 11 g/dl.

The analysis included descriptive statistics on age, sex, hemoglobin concentration, anthropometric measures of the child and mother's education and socio economic status of the family. A 'P' value of less than 0.05 was considered significant. A "paired t" test was used to compare the "before" and "after" hemoglobin change and mean hemoglobin concentration change in each group. "Independent t" test was used to compare the mean hemoglobin concentration change between the groups to assess if there is any superiority among the two intervention groups. Analysis for estimation of mean hemoglobin concentration change and compliance rate estimation has been based on "intention to treat" analysis.

7. Results

The results will be presented as follows:

Objective 1. Effectiveness of the interventions

1. Baseline characteristics of the children
2. Change in the mean hemoglobin concentration by:
    a. intervention group
    b. age and
    c. sex

3. Status of anemia

Change in the status of anemia by:

A. intervention group

B. age

C. sex and severity

Objective 2 : Compliance

4. Compliance rate by:

a. intervention group

b. age

c. sex

d. response

Objective 3

5. Reasons for non-compliance

7.1. Study children

A total of 134 children aged 6 to 35 months met the eligibility criteria and they were randomly allocated to each intervention group of iron with folic acid (IFA) and iron alone. The number of children allocated equally to each intervention group was 67. Out of these, 11(16.4%) and 9 (13.4%) subjects of the respective groups did not receive the specified intervention. The reasons for not participating in the study in both the groups together were fear of finger prick for hemoglobin estimation (n=9), door locked on repeated visits (n=6) and family refused the child's participation (n=5). The number of children who received the respective allocation were 56 in IFA and 58 iron alone group.

Ninety six percent (54/56) in IFA and 98 percent (57/58) in iron alone group adhered to the protocol and were followed up for 100 days. Though followed up for 100 days, analysis could not be done in 2 out of 54 (3.7%) in IFA and 4 out of 58 (6.9%) in iron alone group. One each from the two groups refused to give blood sample at the end of intervention period. One in the IFA and 3 in the iron alone group were unavailable (door locked on repeated visits) at the time of post-intervention hemoglobin estimation. Therefore, analysis has been done in 106 children (52 in IFA and 54 in iron alone group).

7. 1. Baseline characteristics of children

Table 4. shows the baseline characteristics of the children who participated in the study to satrt with.

Iron with folic acid

The mean age (± SD) of the study subjects was 21.7 ± 9.5 months. Males constituted 45% of the total. The mean height (± SD) was 76.2 ± 8.83 cm and the mean weight was 9.41 ± 1.2 kg. The mean birth weight (± SD) was 2.65 ± 0.49 kg. The mean hemoglobin (± SD) concentration (g/dl) was 10.43 ± 1.23.

Iron alone

The mean age ± SD of the study subjects was 23.7 ± 8.9 months. Males constituted 47% of the total. The mean height ± SD was 77.3 ± 8.9 cm and the mean weight ± SD was 9.5 ± 1.8 kg. The mean birth weight ± SD was 2.67 ± 0.44 kg. The mean hemoglobin ± SD concentration (g/dl) was 10.51 ± 1.06.

Table 4. Baseline characteristics of children aged 6 to 35 months by intervention group, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Variables	Intervention group	
	Iron with folic acid (n= 56)	Iron alone (n= 58)
Demographic		
Age (months)	21.7 ± 9.5*	23.1± 8.9
6 –12	19.6 (11)†	12.1 (7)
13 – 24	44.6 (25)	43.1 (25)
25 – 35	35.7 (20)	44.8 (26)
Sex		
Male	44.6 (25)	46.6 (27)
Female	55.4 (31)	53.5 (31)
Anthropometric		
Height (cm)	76.2 ± 8.8	77.3 ± 9.0
Weight (kg)	9.4 ± 2.0	9.5 ± 1.8
Birth weight (kg)	2.7 ± 0.5	2.7 ± 0.4
Mother's education		
No education	23.2(13)	29.3 (17)
Primary or secondary	69.6 (39)	56.9 (33)
>Secondary	7.1 (4)	13.8 (8)
Socio-economic status		
Low	36.5 (20)	37.0 (22)
Intermediate	35.7 (20)	40.2 (23)
High	28.0(16)	22.8 (13)

* Values are means ± SD

† numbers in parentheses are number of children

There were no unusual differences the measured variables at the baseline between the children in the iron alone or iron with folic acid groups (Table 4). Also, no baseline characteristic differed significantly between children aged 6 to 35 months of the selected villages who participated and those who did not participate in the study.

7. 2. Change in mean hemoglobin (g/dl) concentration

The change in mean hemoglobin concentration (g/dl)from baseline to the end of 100 days of intervention is shown in Table 5.

Table 5. Change in mean hemoglobin (g/dl) concentration in children aged 6 to 35 months, at baseline and post-intervention , Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Hemoglobin (g/dl)*	Iron with folic acid (n=52)	Iron alone (n=54)
Baseline	10.1 ± 1.3	10.1 ± 1.4
Post-intervention	11.2 ± 1.4	11.2 ± 1.4
Change	1.1 ± 0.6†	1.1 ± 0.7

*Values are means ± SD
†Paired "t" = 13.2 ; $p < 0.001$; ** Paired t = 11.61 ; $p < 0.001$

The change in mean hemoglobin concentration (g/dl) from baseline to the end of 100 days of intervention was statistically different in both the groups (Table 5) . However, there was no statistical significance in the mean hemoglobin concentration change between the groups ($t = 0.09$; $P = 0.93$).

7.2. 1. Change in mean hemoglobin (g/dl) concentration by sex

The change in mean hemoglobin (g/dl) concentration by sex in both the intervention groups is shown in Table 6.

Table 6. Change in mean hemoglobin (g/dl) concentration in children aged 6 to 35 months by intervention and sex , Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Sex group	Mean Hemoglobin concentration (g/dl)*					
	Iron with folic acid (n=52)			Iron alone (n=54)		
	Baseline	Post-intervention	Change†	Baseline	Post-intervention	Change†
Male	10.4±1.4	11.5±1.5	1.1±0.8	10.1±1.2	11.4±1.4	1.3±0.9
Female	9.8±1.1	11.0±1.3	1.2±0.5	10.1±1.5	11.1±1.5	1.0±0.6

*Values are means ± SD

†significantly different from baseline ($p<0.001$)

The change in the mean hemoglobin (g/dl) concentration by sex was statistically significant in both the intervention groups ($p<0.001$). The change was found to be slightly higher in the males of iron alone group whereas the reverse was true in the females of the iron with folic acid group. However, the change was not statistically significant between the two groups by sex ($P>0.05$).

7. 2. 2. Change in mean hemoglobin (g/dl) concentration by age

The change in the mean hemoglobin (g/dl) concentration by age in both the intervention groups is shown in Table 7.

Table 7. Change in mean hemoglobin (g/dl) concentration in children aged 6 to 35 months by intervention and age , Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Age group	Intervention					
	Iron with folic acid (n=52)			Iron alone (n=54)		
	Baseline	Post-intervention	Change*	Baseline	Post-intervention	Change*
6 –12‡	10.2±1.6	11.4±1.5	1.1±0.5	10.5±1.4	11.2±1.1	0.7±0.4†
13 –24	10.3±1.2	11.4±1.4	1.1±0.7	9.9±1.4	11.1±1.5	1.2±0.7
25 -35	9.7±1.1	10.9±1.3	1.1±0.6	10.1±1.4	11.3±1.5	1.2±0.8

*p<0.001

†p=0.004

‡ Values are means ± SD

The change in the mean hemoglobin (g/dl) concentration was statistically significant in both the intervention groups in all age groups (p<0.001) as well as in the 6 to 12 age group of iron alone group (p=0.004).However, the change was not statistically significant between the two groups by age (P >0.05).

7.3. Status of anemia at baseline

Totally, the proportion of children who were anemic (hemoglobin of less than 11g/dl) at baseline was 70% (74 of 106).

7. 3 .1. Status of anemia by age at baseline

The overall status of anemia by age at baseline is shown in Table 8.

Table 8. Status of anemia in children aged 6 to 35 months by age at baseline, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

	At baseline					
Age	**Anemic**		**Non-anemic**		**Total**	
(months)	**n**	**%**	**n**	**%**	**N**	**%**
6 –12	9	56.4	7	43.8	16	15.1
13 –24	31	70.5	13	29.6	44	41.5
25 - 35	12	73.9	12	26.1	46	43.4

χ^2_{trend} = 0.90; P = 0.34 ; * percentages based on fewer than 25 observations

The proportion of children who were anemic was found to be higher with increasing age. However, this was not statistically significant (p=0.34)

7. 3. 2. Status of anemia by sex at baseline

The status of anemia by sex in both the intervention groups is shown in Table 9.

Table 9. Status of anemia in children aged 6 to 35 months by sex at baseline, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Sex	Anemic		Non-anemic	
	n	%	n	%
Male	30	62.5	17	53.1
Female	44	75.9	15	46.9

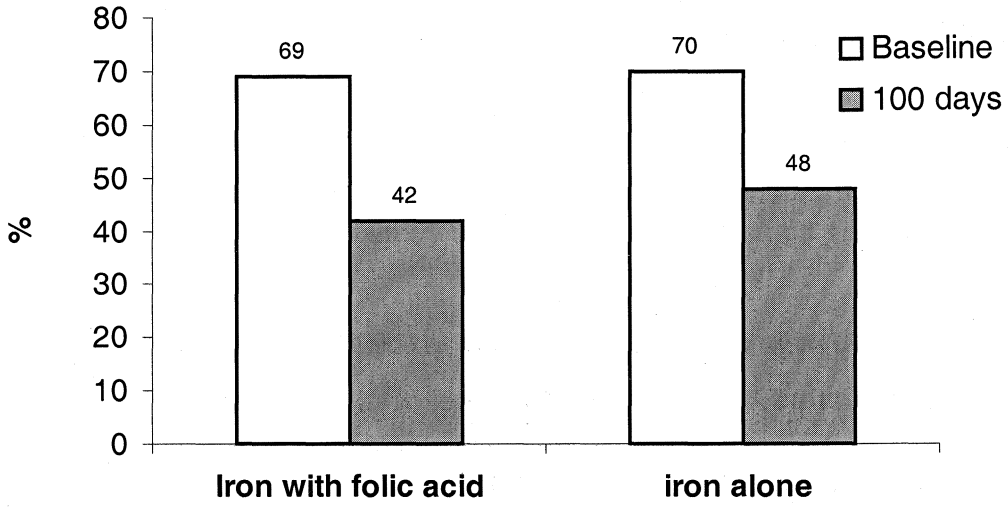
$\chi^2 = 0.97$; P = 0.32

The proportion of overall anemic female chidren (at baseline) was found to be higher than the males. However, this was not statistically significant.

7. 4. Change in the status of anemia by intervention group

The change in the status of anemia in both the intervention groups is shown in Fig 1.

Figure1. Change in the status (%) of anemia at baseline and after 100 days of intervention in iron with folic acid and iron alone groups, 6 to 35 months aged children, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003



The decrease in the prevalence of anemia (hemoglobin of less than 11g/dl) was significant in both the groups. The reduction of anemia was 27% in the iron with folic acid ($\chi^2 = 7.64$; $p = 0.01$) and 22% in the iron alone ($\chi^2 = 5.52$; $p = 0.02$) intervention group. However, this decrease was not significant between the groups ($\chi^2 = 0.32$; $P = 0.57$).

7.4.1. Change in the status of anemia by intervention and age

The change in the status of anemia by age is shown in Table 10

Table 10. Change in the status of anemia in children aged 6 to 35 months by intervention and age, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Age groups (months)	Status of Anemia (%)			
	Iron with Folic acid (n=52)		Iron alone (n=54)	
	Baseline	Post – Intervention	Baseline	Post - Intervention
6-12	40.0 (6)†	20.0 (3)	42.86 (3)	28.57 (2)
13-24	76.5 (13)*	41.12 (7)	85.71 (18)	66.67 (14)
25-35	85.0 (17)	60.0 (12)	61.54 (17)	38.46 (10)

* $\chi^2 = 4.37$; P = 0.04
† numbers in parentheses are number of children

The proportion of children who had a change in the status of anemia from baseline to the post intervention by age was found to be high and statistically significant in the 13 to 24 months of the iron with folic acid group (p=0.04).

7. 4. 2. Change in the status of anemia by sex

The change in the status of anemia by sex in both the intervention groups is shown in Table 11.

Table 11. Change in the status of anemia in children aged 6 to 35 months by intervention and sex, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

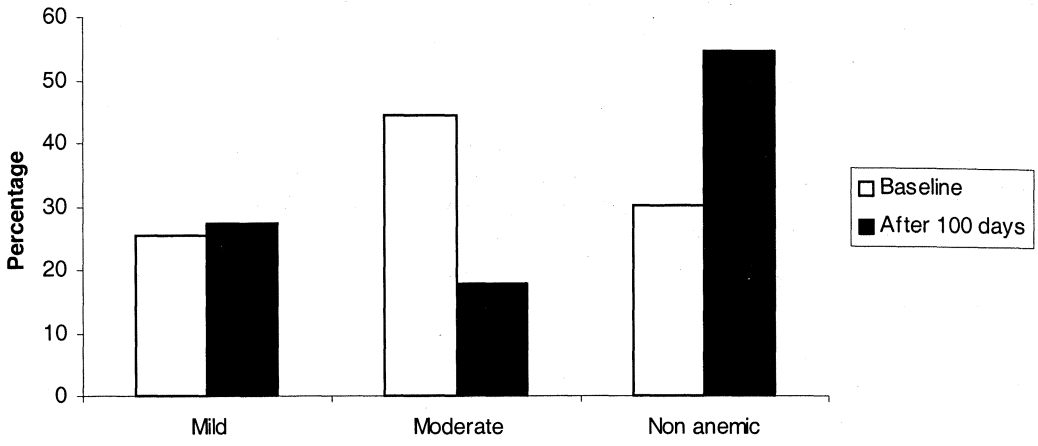
Sex	Status of anemia (%)			
	Iron with folic acid(n=52)*		Iron alone (n=54)*	
	Baseline	Post-intervention	Baseline	Post - intervention
Male	56.52 (13)	34.78 (8)	68.0 (17)†	40.0 (10)
Female	79.3 (23)‡	48.28 (14)	72.41 (21)	68.97 (16)

*numbers in parenthesis are number of children
† $\chi^2 = 3.95$; P = 0.05
‡ $\chi^2 = 6.05$; P = 0.01

The change in the status of anemia was found to be higher in the females ($\chi^2 = 6.05$; P = 0.01) of iron with folic acid and males ($\chi^2 = 3.95$; P = 0.05) of the iron alone group.

The change in the status of anemia by severity is depicted in figure 2

Figure 2. Change in the status of anemia by severity in children aged 6 to 35 months,Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu,2003 (n=106)



There was a 1.9% increase, 26.4% reduction and 24.5% increase in the proportion of children who were mild and moderate anemics and non-anemics at the end of intervention respectively. The reduction of moderate anemics ($\chi^2 = 4.88$; P = 0.03) and increase of non-anemics ($\chi^2 = 4.74$; P = 0.03) was found to be statistically significant.

7. 4. 4. Change in the status of anemia by severity and intervention

The change in the status of anemia by severity in both the intervention groups is shown in Table. 12.

Table 12. Change in the status of anemia by severity in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Severity of Anemia	Status of anemia (%)							
	Iron with folic acid (n=52)				Iron alone (n=54)			
	Baseline		Post-intervention		Baseline		Post-intervention	
	n	%	n	%	n	%	n	%
Mild	12	23.1	12	23.1	15	27.8	17	31.5
Moderate	24	46.2	10	19.2	23	42.6	9	16.7
Non-anemic	16	30.7	30	57.7	16	29.6	28	51.9

A 27% and 25.9% reduction was seen in the proportion of moderately anemic children in the iron with folic acid and iron alone groups respectively. Similarly, 25.9% and 22.3% rise in the proportion of anemics was observed in the respective groups. In both these categories, a slightly higher effect is seen with the use of iron with folic acid.

7. 4. 3. 1. Iron with folic acid

Further analysis of the status of anemia by severity at baseline and post-intervention is shown in Table 13 & 14.

Table 13. Status of anemia by severity at baseline and post – intervention (iron with folic acid) in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Baseline \ After	Non anemic (%)	Mild(%)	Moderate (%)	Total
Non anemic	16 (100)	0	0	16
Mild	10 (83.3)	2 (16.7)	0	12
Moderate	4 (16.7)	10 (41.7)	10 (41.7)	24
Total	30	12	10	52

$\chi^2 = 32.5$; $P < 0.001$

Of all the non-anemics at baseline, none of them became anemic by post-intervention. In the mild anmeic category, 83.3% of them became non-anemic and 16.7% remained mild anmeics. Of the 24 moderately anemic children, 16.7% became non-anemics and 41.7% became mild and 41.7% remained moderate anemics by the end of intervention.

7. 4. 3. 2. Iron alone

Table 14. Status of anemia by severity at baseline and post intervention (iron alone) in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Baseline \ After	Non anemic(%)	Mild(%)	Moderate(%)	Total
Non anemic	16 (100)	0	0	16
Mild	11 (73.3)	4 (26.7)	0	15
Moderate	1 (4.3)	13 (56.6)	9 (39.1)	23
Total	28	17	9	54

$\chi^2 = 40.36$; $P < 0.001$

Of all the non-anemics at baseline, none of them became anemic by post-intervention. In the mild anemic category, 73.3% of them became non-anemic and 26.7% remained mild anemics. Of the 23 moderately anemic children, 4.3 became non-anemics and 56.6% became mild and 39.1% remained moderate anemics by the end of intervention

Objective 3.

7. 5. Compliance Rate

The degree of compliance was classified into three categories by number of days of consumption of the inteventions : (1) more than 80 days, (2) 60-80 days and (3) less than 60 days.

The compliance by intervention groups is shown in Table 15.

Table 15: Compliance by intervention group in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Compliance (No.ofdays) consumed)	**Iron with folic acid (n=52)**		**Iron alone (n=54)**	
	n	**%**	**n**	**%**
More than 80	15	28.8	22	40.7
60-80	30	57.7	24	44.4
Less than 60	7	13.5	8	14.8

$\chi^2_{trend} = 0.65$; P = 0.42

The overall compliance of more than 80 doses administration was slightly higher in the iron alone group (41%) when compared to the IFA group (29%). The compliance in the less than 60 doses category was similar in both the intervention groups.

7. 5. 1. Compliance By Age And Intervention

The compliance by age is showed in Table 16. showed that there was not much difference in the 60 – 80 dose category of the iron with folic acid group.

Table 16. Compliance by intervention group and age in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Age groups (months)	Iron with folic acid (n=52)			Iron alone (n=54)		
	>80†	60-80	<60	>80	60-80	<60
6-12*	30.0 (3)	60.0(6)	10.0(1)	66.6 (4)	16.7(1)	16.7(1)
13-24	31.8 (7)	59.1 (13)	9.1 (2)	40.9 (9)	45.5 (10)	13.6 (3)
25-35	25.0(5)	55.0 (11)	20 (4)	34.6 (9)	50.0 (13)	15.4 (4)

*numbers in parentheses are number of children
† the three categories are no. of days of consumption of supplement

Overall, the compliance rate is higher in the 60 – 80% in all age groups of both the intervention groups except for the 6 to 12 age group of iron alone intervention group.

7. 5. 2. Compliance by sex and intervention

Compliance by sex in both the intervention groups is shown in Table 17.

Table 17. Compliance rate by intervention group and sex in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Sex*	Iron with folic acid (n=52)			Iron alone (n=54)		
	>80	60-80	<60	>80	60-80	<60
Male	31.8 (7)	68.2 (15)	0	40.0(10)	44.0 (11)	16.0 (4)
Female	26.5 (8)	68.2 (15)	23.3 (7)	41.4 (12)	44.8 (13)	13.8 (4)

*numbers in parentheses are number of children

The compliance rate was found to be slightly different in the more than 80 doses category in the two intervention groups between males and females. There was no

difference in the compliance rate between the sexes in the IFA group of 60 to 80 doses and a marginal difference in the iron alone group. The females of the IFA group had a higher non-compliance rate in the IFA group whereas there was not much difference in the iron alone group between the sexes.

6. 5. 3. Compliance by status of anemia (post-intervention)

The compliance by status of anemia at post – intervention in both the groups is shown in Table 18.

Table 18. Compliance rate by post intervention hemoglobin status and intervention in children aged 6 to 35 months, Thimmavaram village, Saidapet Health Unit District, Tamilnadu, 2003

Compliance	Iron alone (n=54)				Iron with folic acid (n=52)			
	NA* (%)	Mild (%)	Moderate (%)	Total	NA (%)	Mild (%)	Moderate (%)	Total
>80	12 (54.6)	8 (66.7)	2 (16.7)	22 (40.7)	14 (93.3)	1 (0.7)	0	15 (28.8)
71-80	11 (57.9)	6 (31.6)	2 (10.5)	19 (35.2)	10 (55.6)	5 (27.8)	3 (16.6)	8 (34.6)
61-70	3 (60.0)	0	2 (40.0)	5 (9.3)	4 (33.3)	5 (41.7)	3 (25.0)	12 (23.0)
51-60	2 (33.3)	2 (33.3)	2 (33.3)	6 (11.1)	2 (33.3)	1 (16.7)	3 (50)	6 (11.5)
<50	0	1 (50.0)	1 (50.0)	2 (3.7)	0	0	1 (100)	1 (1.9)
Total	28	17	9	54	30	12	10	52

*Non anemic

The compliance (in days) when classified further and analysed by status of anemia at post-intervention showed that 93% (14/15) and 55% (12/22) of the non - anemics in the IFA and iron alone groups had more than 80 doses. The compliance had significant association with the post intervention anemic status in the IFA group (χ^2= 19.3; P=0.01) whereas it was not the case in the iron alone group.

7. 5. 4. Compliance by responders

The responders were classified as those who had a more than 1g/dl rise in the hemoglobin concentration. The compliance was classified into three groups as described earlier. There was not any statistical significance between the groups by response and compliance (Table 19).

Table 19. Compliance rate by response (more than 1g/dl) in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Compliance (in days) ((in (in days)(days)	Iron with folic acid (n=32)			Iron alone (n=30)		
	Responders n (%)	Non responders n (%)	Total n (%)	Responders n (%)	Non responders n (%)	Total n (%)
More than 80	10 (66.7)	5 (33.3)	15 (28.8)	13 (59.1)	9 (40.9)	22 (40.7)
60-80	21 (70.0)	9 (30.0)	30 (57.7)	13 (54.2)	11 (45.8)	24 (44.4)
Less than 60	1 (16.7)	6 (83.3)	7 (13.5)	4 (50)	4 (50)	8 (14.8)

The proportion of children who responded to the intervention with a rise of 1g/dl was higher in the more than 80 category of the iron alone group and in the 60 –80 category of iron with folic acid group. The proportion of children who were non-responders was high in the less than 60 category of iron with folic acid . An equal distribution of responders and non-responders was found in the less than 60 doses category with the iron alone group.

Further analysis of response by classifying the compliance rate into five categories of more than 80, 71 to 80, 61 to 70, 51 to 60 and less than 50 also did not show any statistically significant difference in both the intervention groups.

7. 5. 4. Reasons for non-compliance

The reasons for non-compliance is shown in Table 20.

Table 20: Reasons for non-compliance in children aged 6 to 35 months, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Reasons[1]	Iron with folic acid (n= 37)		Iron alone (n=32)	
	n	%	n	%
Forgotten	37	100	32	100
Fever	25	67.6	22	68.8
Upper respiratory infections	27	73.0	26	81.0
Went to relatives home	13	35.1	9	28
Child refused	4	10.8	2	6.3
Vomiting	1	2.7	0	0
Diarrhoea	1	2.7	1	3.1
Broken/Spillage	4	10.8	2	6.3

Any mother who gave the above mentioned reasons in more than one occasion on repeated follow up visits has been taken into consideration for that specific cause of reason. Therefore, one mother might be appearing in more than one reason.

The reasons for non-compliance were gathered from the mothers / guardians once in every five days and was later on compiled as per the arbitary classification of non compliers i.e. those who had given less than 81 doses of the supplement to their respective children / wards. All these mothers gave the reason "forgotten" to administer the supplement (Table 20). This was followed by the "child being ill" (fever, upper respiratory tract infections) about 70 and 75% respectively in both the intervention groups.Reasons related to the child's refusal to take the supplement was 10.8 and 6.3% in iron with folic acid and iron alone group. The most common reported side effects which were commonly associated with iron intake were very minimal in this study – only one child of iron with folic acid reported vomiting and one each of both the groups reported diarrhoea.

8. Discussion

Iron deficiency anemia is a major public health problem in children below three years of age which often goes un-noticed in the early stages of life. In this current study, 106 children were followed up for 100 days. The baseline hemoglobin estimation showed that the prevalence of anemia was 70%. This high prevalence of anemia is consistent with other studies conducted in different settings of India[7-9,13,14,18] and the NFHS II(1998– 1999)[21] data. The proportion of anemic children increases with the advance of age which is consistent with the MMWR weekly report[69] (1998). It was also observed that anemia is higher in female children. The absence of statistical significance could be due to small numbers.

8. 1. Change in the mean hemoglobin (g/dl) concentration

In both the intervention groups , there was a statistically significant increase in the mean hemoglobin (g/dl) concentration level at the end of 100 days when compared to that of the corresponding baseline mean hemoglobin (g/dl) concentration. However , the increase was not statistically significant between the groups.

The increase in hemoglobin concentration with the supplementation of Iron III Hydroxide Polymaltose Complex is consistent with other studies[92,93,96-98] (Table 22). Reviewed literature shows that only two comparative studies have been conducted: one each in infants[93] and in children[98] using Iron III hydroxide Polymaltose Complex and Ferrous sulphate. One non comparative trial[97] using Iron III Hydroxide Polymaltose Complex with

folic acid has been undertaken in adults which again shows an increase in the hemoglobin concentration at the end of 12 weeks of intervention.

Table 21. Studies showing change in hemoglobin (g/dl) in various settings, age groups and different forms of supplementation

Study area	Type of iron supplement	Days of supplementation
Children		
Mexico[93]	IPC, Ferrous sulphate	60
Pauline school of Medicine[98]	IPC, Ferrous sulphate	60
Adults		
Pune[97]	IPC + Folic acid	12 weeks
Switzerland[92]	IPC, Ferrous sulphate	9 weeks
Pregnant women		
Kolhapur[96]	IPC, Ferrous fumarate	30

8.2. Addition of folic acid to iron supplementation

The current study has not shown any significant difference in the increase in the hemoglobin concentration between both the intervention groups. This finding of non significant increase in hemoglobin concentration is consistent with other studies[85-91]. The issue of adding folic acid as a routine to iron supplementataions can be questioned with this finding. However, it was evident from analysis that in the IFA group, higher compliance leads to higher response i.e rise in hemoglobin concentration by 1g/dl . Similarly, the compliance has got a direct association with the change in the anemic status of the children at post intervention in the IFA group. Therefore, the role of folic acid (in iron suplementations) on reducing/ correcting the anemia status as well as the possible favourable impact on various other variables like growth, psycho motor development in the long run has to be kept in mind before coming to any conclusion.

8.3. Side effects and compliance

Literature review has shown that the main limitation of the National Anemia Control Programme is poor compliance due to difficulty in swallowing of the tablets[37,38]. The

observed good compliance (70 and more doses) of 76% and 63% in the iron alone and IFA groups respectively suggests that liquid iron supplementation should be preferred in the National Programme.There were no self reported side effects like nausea or abdominal pain Other side effects like vomiting and diarrhoea were minimal. There was no incidence of staining of teeth which is consistent with the Switzerland study[92]. The apparent high compliance might have been due to the following factors:

1. Better acceptance of the liquid form

2. Social mobilisation done prior to the launch of the project

3. Training and education of the mothers which again was done beforehand

4. Constant monitoring by the investigators

5. Decreased side effects

8. 4. Cost of Iron III Hydroxide Polymaltose Complex

The direct cost (MRP) of one dose per child per day amounts to about 67 paise and 52 paise for the iron alone and iron with folic acid supplementations as opposed to the earlier high cost.. Re-introduction of liquid iron as a supplement in the National Nutrition Anemia Control Programme Prevention may be considered as the long term benefits of a socially acceptable form of intervention may far outweigh the higher cost when compared to the tablet forms. Moreover, as there is an existing national programme, the supplementation administration and constant monitoring can be maintained with ease with no further added expenses to the Government.

9. Limitations Of The Study

9. 1. Internal validity

Information bias

The reported compliance and side effects were monitored once in five days for the whole study duration. During each visits, entries were made as per the responses given by the mother. There is a possiility of under or over reporting which has to be considered. Though compliance was measured in terms of remaining liquid once in five days, the unmonitored wastage due to spilling or administration of more than the required dosage of the supplement in one single day itself or sharing with other children of the family the could not be accounted for. The actual amount of consumption of supplement per day per child is not known.

9. 2. External validity

1. The study has been done under controlled conditions of close supervision and monitoring by the field investigators. A study of compliance under routine programme conditions needs to be investigated.

2. Larger studies need to be undertaken before generalisation could be done as this is a study on relatively small sample.

10. Recommendations

- The better compliance and relativelely few side effects of Iron III hydroxide Polymaltose Complex in liquid form when compared to other liquid ferrous forms and tablets suggests that it may be considered as the iron supplement of choice under the National Anemia Control Programme to under three children.

- The existing infrastructure can be strengthened by making utilisation of the services of ICDS workers as this target group of children aged 6 to 35 months has direct contact with these people.

11. Conclusion

To conclude, iron deficiency anemia is a major public health problem in Tamilnadu more so in children aged 6 to 35 months. Liquid Iron III hydroxide Polymaltose Complex can be considered as the supplementation of choice under the National Anemia Control Programme to under three children.

Concentrated multi dimensional efforts should be made in the near future to combat this major concern. The cost effectiveness and acceptability of various interventions by the community under programme conditions has to worked out . Further studies are needed to identify the prevalence of folic acid deficiency in Tamilnadu and to study the long term implications of addition of folic acid to iron supplements.

12. References

1. INACG/WHO/UNICEF. Guidelines for the use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia, Washington. D.C., 1988
2. United Nations Administrative Committee on Coordination Sub-Committee on Nutrition. Fourth Report on the World Nutrition Situation, ACC/SCN/IFPRI. Geneva.2000
3. WHO. Malnutrition.The Global Picture, World Health Organization, Geneva.2000
4. DeMaeyer E, Adiels-Tegman M. The prevalence of anemia in the world. World Health Stat Q 1985;38:302–16
5. ACC/SCN. Second report on the world nutrition situation. Global and regional results. Vol 1. Geneva: ACC/SCN. 1992.
6. Roodenburg AJ. Iron supplementation during pregnancy. Eur JObstet Gynecol Reprod Biol 1995;61:65–71.
7. Dhar N, Agarwal KN,Taneja PN,Gupta S. Iron deficiency anaemia in children. Indian J Pediatr 1969:36:436 –441.
8. Studies on preschool children. ICMR Tech Rep Ser No 26.National Institute of Nutrition. Hyderabad .1977
9. Uberoi IS,DeSweemer C,Taylor CE.A story of anaemia among rural Punjabi children.Indian J Med Res. 1972;60:793-799.
10. Agarwal DK,Bharadwaj B,Singla P,.Tripathi AM,and Agarwal KN. Etiology of maternal and early childhood deciency anaemia. Indian J Paediatr. 1986;53:389-396.
11. Raman L,Pawashe AB,Vasanthi G,Parvathi CH,Vasumathi N, Rawal.A.Plasma ferritin in he assessment of iron status on Indian infants.Indian Paediatr. 1990;27:705-713.
12. Raman L, Pawashe AB, Ramalakshmi BA.Iron nutritional status of pre school children. Indian J Paediatr. 1992;59:209-212.
13. Kapur D,Agarwal KN, Sharma S, Kaur I. Iron status of children aged 9-36 months in an urban slum Integrated Child Development Services [ICDS] Project in Delhi. Indian J Paediatr. 2002;54:312-316.

14. Gomber S,Kumar S,Rusia U,Agarwal KN,Sharma S,Prevalance and etiology of nutritional anaemias in early childhood in an urban slum.Indian J Med Res. 1998;107:269-73.

15. Singla PN, Gupta HP,Ahuja C,Agarwal KN. Deficiency anemias in preschool children- Estimation of prevalence based on response to hematinic supplementation. J Trop Paediatr. 1982; 28:77-80.

16. Nestel P, David A. editors. Iron/multi micronutrient supplements for young children Summary and conclusions of a consultation; UNICEF, Copenhagen; 1996 August 19-20; UNICEF, Copenhagen. USA: John Snow Inc; 1997.

17. FAO/WHO. Report of a joint FAO/WHO expert consultation: requirements of vitamin A,iron,folate and vitamin B_{12}. FAO Food and Nutrition Series No 23, Rome, 1988

18. Malin AS, Stones RW, Nutritional anaemia in the urban poor:a community – based study of under fives in an Indian slum.J Trop Paediatr. 1988;34:257-259.

19. Institute of Medicine, Nutrition during Pregnancy, Washington, D.C, National Academy Press, 1990.

20. Gillespie S & Johnston J.Expert consultation on Anemia Determinants and Interventions. Ottawa: The Micronutrient Initiative. 1998

21. NFHS (2000) India 1998-99 - National Family Health Survey-2 (NFHS-2)- Key findings: Anemia among women and children. International Institute for Population Sciences, Mumbai, 2000

22. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievements among school aged children and adolescents in the United States. Pediatrics .2001; 6 (107): 1381-1386.

23. Pollitt E. Iron deficiency anemia and cognitive function. Ann Rev Nutr . 1993; 13: 521-537.

24. Scrimashaw N. Functional Significance of Iron Deficiency. *In:* Functional Significance of Iron Deficiency. Third Annual Nutrition Workshop. Eds. Enwonwu C. Meharry Medical College, Nashville, TN, USA, 1990, pp 1-14.

25. Soemantri A G, Pollitt E & Kim I. Iron deficiency anemia and educational achievement. Am. J. Clin. Nutr. 1985;42: 1221–1228.

26. Soewondo S, Husaini M. & Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children. Bandung, Indonesia. Am. J. Clin. Nutr. 1989;50: 567–574.

27. Lozoff B, Jimenez AW. Long term development outcome of infants with iron deficiency. New Engl J Med. 1991; 325: 687-694.

28. Preventing Iron defieincy in women and children technical consensus on Key Issues. 7-9 October 1998, UNICEF, UNU, WHO, MI, Technical Group International Nutrition Foundation, USA 1998.

29. Agarwal K N. Iron and brain: neurotrasmitter responses and magnetic response spectroscopy. Brit J Nutr . 2001; 85 Suppl 2 S147 – 150

30. Beard J, RJ Stolzfus . Iron-deficiency anemia: Reexamining the nature and magnitude of the public health problem. Journal of Nutrition. 2001;131. 2S-II.

31. Draper A. Child development and iron deficiency: USAID. Opportunities for Micronutrient Interventions and partnerships for Child development 1997; Washington DC

32. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med. 1991; 325:687-94.

33. Gibson R.S, FergusonE L. Complementary foods for infant feeding in developing countries:their nutrient adequacy and improvement. Eur.J.Clinical Nutr. 1998; 52(10):764.

34. Stoltzfus R, Dreyfuss M. Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia. The International Nuritional Anemia Consultative Group Washington, D.C., USA, 1998.

35. Zlotkin S. Current issues for the prevention and treatment of iron deficiency anemia. Indian Pediatr .2002; 39: 125-128.

36. Allen et al. Lack of hemoglobin response to iron supplementation in anemic Mexican preschoolers with multiple micro nutrient deficiencies . Am J Clin Nutr. 2000; 71: 1485 – 94.

37. Indian Council of Medical Research. Evaluation of the National Nutritional Anemia Prophylaxis Programme -An ICMR task force study. New Delhi: Indian Council of Medical Research: 1989.

38. Schultnik W. Iron supplementation: compliance of target groups and frequency of tablet intake. Food Nutr Bull. 1996;17: 22-6.

39. Jacobs P, Wood L, Bird AR. Better tolerance of iron polymaltose complex compared with ferrous sulphate in the treatment of anemia. J Haematology. 2000; 5: 77-80

40. Brock C, Curry H. Comparative incidence of side effects of a wax matrix and sustained release iron preparation. Clin ther. 1985; 7:492 – 496.

41. Geisser P, Muller A. Pharmacokinetics of iron salts and ferric hydroxide-carbohydrate complexes. Drug Res. 1987; 37(1A):100-4.

42. Baumgartner JA. Clinical overview of studies regarding the safety of iron polymaltose complex. (Toxicity, iron overloading) 1997.

43. Jacobs P. Oral iron therapy in human subjects: comparative absorption between ferrous salts and iron poly maltose. J Medicine. 1984; 3: 387-377

44. Jacobs P,Wormland L, Gregory M.Absorption of iron polymaltose and ferrous sulphate in rats and humans. S Afr Med J. 1979; 55:1065.

45. Kaltwasser JP. Bioavailability and therapeutic efficacy of bivalent and trivalent iron preparations. Arneim / forsch / Drug Head of Cattle. 1987; 37 (1): 122.

46. Geisser P. Invitro studies on interactions of iron salts and complexes with food stuffs and medicaments. Drug Res. 1990; 40:754

47. Schmidt B J, Morais M B, Fisberg M, Martins A, Machado N L. Comparison of ferrous sulphate and trivalent iron in the form of a polymaltose ferric hydroxide complex in the treatment of organic iron deficiency (English version) Separata de Folha Medica. 1985; 90(4) .

48. YipR.Iron deficiency:contemporary scientific issue and international programmatic approaches, Journal of Nutrition. 1994; 124, 1479S.

49. DeMaeyer E., Preventing and controlling iron deficiency anemia through primary health care. A guide to health administrators and programme managers, World Health Organization. 1989; Geneva.1989

50. Hercberg S. Relationship between anemia, iron and folacin deficiency, hemoglobinopathies and parasitic infection. Hum.nutr.Clinical Nutr. 1986; 40,371.

51. HughesER.. Human iron metabolism in Metal Ions in Biological Systems: Iron in Model and Natural Compounds, chap 9,Vol.7, Siegel, H., Marcel Dekker, New

York, 1977.38. Patek A.J. and Health CW. Chlorosis. JAmer Med Assoc.1986; 106,1463.

52. Patek AJ, Health CW. Chlorosis. J Amer Med Assoc.1986; 106:1463.

53. Beard JL, Dawson H. and Pinero DJ. Iron metabolism: a comprehensive review, Nutr. Rev. 1996;54,295

54. Rybo E. Diagnosis of iron deficiency. Scand J Haematol.1985; 43,1

55. Royston E. The prevalence of nutritional anemia in women among developing countries: a critical review of available information, World Health Statistics 1982; Q.,35, 52.

56. WHO . The prevalence of nutritional anemia in women. WHO/MCH 92.2, World Health Organization , 1992, Geneva.

57. Seshadri S, Hirode K, Naik P, Shah A, Gupta N. An effective intervention to reduce the prevalence of anemia in children. Indian J Med Res. 1984; 80: 164-173.

58. Choudhury P, Vir S. Prevention and strategies for control of iron deficiency anemia. *In:* Nutrition in Children, Developing Country Concerns. Editors. Sachdev HPS and Choudhury P, NewDelhi, 1st ed. New Delhi, 1994. p 492-524.

59. Food and Nutrition Board, Government of India, UNICEF. The use of common salt fortified with iron. The report on collaborative studies. Government of India, New Delhi, 1981.

60. Visweswara Rao K, Radhaiah G, Raju SVS. Association of growth status and prevalence of anemia in pre school children. Indian J Med Res. 1980; 71: 2337 – 2346.

61. ACC/SCN. Controlling iron deficiency. ACC/SCN state of the art series. Nutrition Policy Discussion Paper No 9. Geneva, 1991.

62. Dallman PR, MA Siimes, A Stekel. Iron deficiency in infancy and childhood. American Journal of Clinical Nutrition, 32, 86-118, 1980

63. Simes MA, Salmenpera L, Perheentupa J. Exclusive breast feeding for 9 months: risk of iron deficiency. J Paediatr. 1984 ; 104 : 196-199.

64. Ohls RK. Evaluation and treatment of anemia in the neonate, editors. Christensen RD, Saunders WB, Philadelphia, 2000, pg 137

65. Hytten FE, Chamberlain G, editors. Placental transfer. In: Clinical Physiology in Obstetrics. Oxford:Blackwell Scientific Publications, 1980.

66. Slimes MA. Iron nutrition in low birth weight infants.editor. Stekel A,Iron nutrition in infancy and childhood .NewYork : Raven press pp: 75-91, 1984.

67. Blot I, Diallo D, Tchemia G. Iron deficiency in pregnancy : effects on the new born. Current opinions , Hematol. 1999; 6 (2) : 65.

68. Colomer J, Colomer C, Guttiarez D, Jubert A, Nolasco A, Donat J et al . Anemia during pregnancy as a risk factor for infant iron deficiency: Report from the Vatican Infant Anemia Cohort (VIAC) study. Paediate perinatal epidemiol. 1990; 4 (2): 196.

69. Recommendations to prevent and control iron deficiency in the United States. MMWR Morb Mortal Wkly Rep. 1998; 47(RR-3): 1.

70. Grajeda R., Perez-EscamillaR. and Dewey K.G. Delayed clamping of the umbilical cord improves hematalogical status of Gautamelan infants at 2 months of age Am.J.Clinical Nutr. 1997; 65:425.

71. Draper A. Child Development and Iron Deficiency: Early Action is Critical for Healthy Mental, Physical, and Social Development. 1997

72. Rosslyn VA: United States Agency for International Development, Partnership for Child Development, International Life Sciences Institute, Opportunities for Micronutrient Interventions,1997

73. Pollitt E. Early iron deficiency anemia and later mental retardation. American Journal of Clinical Nutrition. *1999;* 69: 4-5.

74. Viteri F E. Iron deficiency. In: Proceedings of ending hidden hunger. Montereal, Quebec,Canada, October 1991, 10-12.

75. Chandra RK and Saranya AK. Impaired immunocompetence associated with iron deficiency. J Pediatr. 1975; 86:899.

76. Thibault H., Galan P, Seltz F, Preziosi P, Olivier C, Badoual J and Hercberg S. The immune response in iron deficient young children: effect of iron supplementation on cell- mediated immunity. EurJPediatr. 1993; 152, 120.

77. Domellof M, Cohen RJ, Dewey KG, Hernell O, Rivera LL, Lonnerdal B. Iron supplementation of breastfed Honduran and Swedish infants from 4-9 months of age. J Pediatr. 2001; 138(5) : 679-687.

78. Beaton GH , McCabe GP. Efficacy of intermittent iron supplementation in the control of iron deficiency anemia in developing countries .The Micronutrient Initiative. Canada, 1999

79. Zlotkin SH, Arthur P, Antwi KY, Yeung G. Randomized controlled trial of single versus three times daily ferrous sulphate drops for treatment of anemia. J. Pediatrics. 2001; 108: 613-616.

80. Canada Health and Welfare. Nutrition recommendations: the report of the Scientific Review Committee. Ottawa: Ministry of Supply and Services,1990.

81. Stevens D, Burman D, Strelling MK, Morris A. Folic acid supplementation in lowbirth weight infants. J Pediatrics. 1979; 64: 333-335.

82. Worthington-White D.A, BehnkeM and GrossS. Premature infants require additional folate and Vitamin B12 to reduce the severity of prematurity. Am.J.Clinical nutr. 1994; 60:930.

83. Mahomed K. Folate supplementation in pregnancy, Cochrane Database of Systematic Reviews,1997

84. Charoenlarp P. A WHO collaborative study on iron supplementation in Burma and thailand. AmJClinical Nutr. 1988; 47:280.

85. FlemingAF, Martin JD, Hahnel R, Westlake AJ. Effects of iron and folic acid supplements on maternal hematology and fetal well being. Med.J.Aust. 1974; 2:429.

86. Batu AT, ToeT, Pe H and Nyunt KK. A prophylactic trial of iron and folic acid supplements in pregnant Burmese women. IsrJMedSci. 1976; 12:1410.

87. Sood SK, RamachandranK, MathurM.. WHO sponsored collaborative studies on nutritional anemia in India: 1. The effects of supplemental oral iron administration to pregnant women. QMedJ. 1975; 44: 241.

88. Iyengar L , Apte SV. Prophylaxis of anemia in pregnancy. AmJClinical Nutr. 1970; 23:725.

89. Jackson RT and Latham MC. Anemia of pregnancy in Liberia, West Africa: a therapeutic trial. AmJClinical nutr. 1982; 35: 710. 85. Osifo B. The effect of folic acid and iron in the prevention of nutritional anemias in pregnancy in Nigeria. Br J Nutr. 1970; 24; 689.

90. Osifo B. The effect of folic acid and iron in the prevention of nutritional anemias in pregnancy in Nigeria. Br J Nutr. 1970; 24; 689.

91. Sirisupandit S. . A prophylactic supplementation of iron and folate in pregnancy, Southeast Asia. J Trop Med Public health. 1983; 14 ; 317.

92. Langstaff RJ, Geisser P, Heil WG, Bowdler MA. Treatment of iron deficiency anemia: A lower incidence of adverse effects with Ferrum Hausmann than ferrous sulphate. Brit J Clin Res. 1993; 4: 191-198

93. José Rafael Borbolla, Ricardo E Cicero, Miguel Dibildox, David Sotres, Rafael Gutiérrez G. Ferric Polymaltose Complex versus ferrous sulphate in the treatment of iron deficiency anemia in infants. Revista Mexican De. 2000; 67(2): 63 – 67.

94. Tomi- Pekka Tuomainen , Kristina Nyyssonen, Elina Porkkala- Sarataho, Riita Salonen, Jessica A. Baumgartner, Peter Geisser, Jukka T Salonen. Oral iron supplementation with ferrous sulphate but not with non ionic iron polymaltose complex increases the susceptibility of plasma lipoproteins to oxidation : Nutr Research . 1999; 19 (8):. 1121 –1132.

95. Report. Study of existing system of procurement, distribution and management of drugs under the national nutritional anemia prophylaxis programme and the national programme for prevention of nutritional blindness due to vitamin A deficiency in selected states of India. Union Ministry of Health and Family Welfare, Govt. of India. 1991

96. Walawalkar SS, Chugh S. A randomized, controlled trial of Ferric hydroxide Polymaltose Complex and Ferrous Fumarate in Pregnancy. JAMA India – The Physician's Update. 2001; 4 (12)

97. Amin RB, Simmerpreet S. An open trial to assess Ferric Hydroxide Polymaltose Complex Plus Folic acid in Iron Deficiency Anemia. JAMA India – The Physician's Update. 2001; , Vol. 4, No.10 (reprint). 1

98. Schmidt B J, Morais M B, Fisberg M, Martins A, Machado N L. Comparison of ferrous sulphate and trivalent iron in the form of a polymaltose ferric hydroxide complex in the treatment of organic iron deficiency (English version) Separata de Folha Medica. 1985; 90(4) .

Appendix 1. Informed Written Consent form

The National Institute of Epidemiology, Chetput, Chennai – 31

"Effectiveness of iron alone and iron and folic acid in liquid form on hemoglobin status of children aged 6 to 35 months, Thimmavaram village, Saidapet Health Unit District, Tamilnadu, 2003"

Information Sheet

Name of the individual	ID No
Name of the mother/father/guardian	Village name
PHC name	District name

Purpose of the study:

Anemia in children of the age group 6m-36 months is a major public health problem. The aim of this study is to find out the effectiveness of liquid iron syrup on the hemoglobin status of this age group after 100 consecutive days of intervention and also estimate the compliance rate amongst this group. By this study, we hope to bring about changes in the implementation strategy of anemia prophylaxis programme of the state over a period of time.

Procedure:

If you agree for your child/ward to participate in this study, our research team will take a blood sample by finger prick method for hemoglobin estimation both initially and at the end of 100 days of treatment free of cost. If it is found that your child/ward is severely anemic, we would be refering your child/ward to the concerned PHC for further therapeutic treatment. Otherwise your child/ward will be getting the liquid iron preparation at the dose of 2 ml/day for 100 consecutive days.

In the meanwhile, our research team members/Village Health Nurse(VHN) will be administering questionnaires to find out the compliance rate of your child. If you need any clarification or more information at any point of time, please feel free to contact the interviewers or the local VHN Mrs. Hilda Devakumari.

Voluntary:

Your child/ward's participation in the study is completely voluntary. You are free to refuse to participate at any time or skip any particular question you do not wish to answer. No force will be applied. The information you have provided and the information we get from the study will be kept strictly confidential.

Risk:

Except for the finger prick for hemoglobin estimation, there will be no physical risk involved by participating in the study. However, the liquid iron preparation is known to have produced mild gastric irritation in some children.

Benefits:

Your child/ward's participation in the study may help us to estimate the effectiveness of the liquid iron preparation on the hemoglobin status of the children in the age group of 6m to 36 months. Your child/ward will benefit from the administration of the intervention and the results of the laboratory investigation will be made available free of cost.

If you agree for your child/ward to participate in the study, please sign/put your left thumb impression in the place mentioned.

I have read the above information/the information has been read to me in my own language. I have had an opportunity to ask questions and the questions that I have asked, have been answered to my satisfaction. I consent voluntarily for my child/ward to participate in this intervention study. I also agree to give my child's/ward's blood sample for the estimation of hemoglobin.

Name of the mother/father/guardian

Signature/thumb impression (mother/father/guardian)

Name of the interviewer

Signature of the interviewer

Place

Date

The National Institute of Epidemilogy
Chetpet, Chennai.

குழந்தையின் பெயர் : தனி நபர் எண் :

கிராமத்தின் பெயர் : திம்மாவரம்

ஆரம்ப சுகாதார நிலையம் : ரெட்டி பாளையம்

மாவட்டம் : சைதாப்பேட்டை

மாநிலம் : தமிழ்நாடு

ஆராய்ச்சியாளரின் பெயர் :Dr. S. பார்வதி

"6 முதல் 35 மாதத்திற்கு உட்பட்ட குழந்தைகளில் இரும்புச்சத்து (திரவ வடிவம்) உட் கொள்வதின் மூலம் இரத்தத்தில் ஏற்படும் ஹீமோகுளோபின் அளவின் மாற்றம்" – சைதாப்பேட்டை மாவட்டம், தமிழ்நாடு, அறியும் ஆய்வில் பங்கேற்க இணங்கும் குழந்தைகளின் பெற்றோர் / பாதுகாவலரின் தகவல் படிவம்.

இந்த ஆய்வினை மேற் கொள்ளும் Dr. S. பார்வதியாகிய நான் நேஷனல் இன்ஸ்டிட்யூட் ஆஃப் எபிடெமியாலஜி சேத்துபட்டு சென்னையில் முதுகலை ஆராய்ச்சி மேறபடிப்பு படித்துக் கொண்டுள்ளேன். இந்த ஆய்வினில் 6 முதல் 35 மாதத்திற்கு உட்பட்ட குழந்தைகளில் இருக்கக் கூடிய இரத்த சோகை பிரச்னை குறித்து ஆய்வு மேற்கொள்ள இருக்கிறோம்.

ஆய்வின் நோக்கம்

எல்லா வயதினர்களிலும் குறிப்பாக 6 மாதம் முதல் 35 மாதத்திற்கு உட்பட்ட குழந்தைகளில இரத்த சோகை ஒரு மிகப்பெரிய பொது சுகாதாரப் பிரச்னை ஆகும். இந்த வயது குழந்தைகளில் இரத்த சோகை இருப்பின் அது அக்குழந்தைகளின் வளர்ச்சியினை பாதிப்பதாக ஆய்வு அறிக்கைகள் கூறுகின்றன. எனவே இந்த ஆய்வினை மேற் கொள்வதின் மூலம் உங்கள் ஊரில் இரத்த சோகை இருக்கும் குழந்தைகளின் (6 - 35 மாதத்திற்கு உட்பட்ட) சதவிகிதத்தை அறிய இயலும். மேலும் இந்த வயது குழந்தைகளுக்கு இந்த ஆய்வின் மூலம் அளிக்கப்பட்ட உள்ள இரு வகையான திரவ

இரும்புச்சத்து மருந்துகளில் ஏதேனும் ஒன்று தொடர்ந்து 100 நாட்கள் கொடுப்பதன் மூலம் இரத்த ஹீமோகுளோபின் அளவில் ஏற்படும் மாற்றத்தைக் கண்டுபிடிக்க இயலும்.

ஆய்வின் செயல்முறை

மேற்கூறிய ஆய்விற்கு குழந்தைகளின் பெற்றோர் / பாதுகாவலரின் தன்னார்வ பங்கேற்பும் ஒப்புதலும் வரவேற்கப்படுகிறது. உங்கள் குழந்தை பங்கேற்பதை நீங்கள் விரும்பினால் முதலில் மருத்துவ பரிசோதனை செய்யப்படும். இப்பரிசோதனையில் குழந்தை மிகவும் உடல் நல குறைவுடன் இருப்பதாக கண்டறியப்பட்டால் அருகில் உள்ள ரெட்டிப்பாளையம் ஆரம்ப சுகாதார நிலையத்திற்கு மேல் மருத்துவ பரிசோதனை மற்றும் கவனிப்பிற்கு பரிந்துரை செய்யப்படும். பின்னர் பெற்றோர் / பாதுகாவலரின் ஒப்புதல் பெறப்பட்ட இதர குழந்தைகளிடம் தேர்ந்த பரிசோதனைக்கூட ஆய்வாளர்களால் ஒன்று (அ) இரண்டு துளி இரத்தம் பரிசோதனைக்கு எடுக்கப்படும். இப்பரிசோதனையில், குழந்தை மிகவும் இரத்த சோகை கொண்டு இருப்பதாகக் கண்டறியப்பட்டால், அருகிலுள்ள ஆரம்ப சுகாதார நிலையத்திற்கு உடனடியாக மேற்படி மருத்துவ கவனிப்புக்கு அனுப்பப்படும்.

ஏனைய தகுதியுடைய குழந்தைகள் ஒவ்வொருவருக்கும் இருவகை திரவ இரும்புச்சத்து மருந்துகளில் ஏதேனும் ஒரு வகை தொடர்ந்து 100 நாட்களுக்கு உங்களாலேயே வழங்கப்படும். இந்த இருவகை மருந்துகளுமே குழந்தைகளிடையே காணப்படும் இரத்த சோகையினை குறைப்பதாக கண்டறியப்பட்டுள்ளது. 100 நாட்களின் முடிவில் ஹீமோக்குளோபின் அளவின் மாற்றத்தைக் கண்டறிய மீண்டும் ஒரு முறை இரத்தப்பரிசோதனை செய்யப்படும்.

உங்கள் குழந்தை சம்பந்தப்பட்ட விவரங்களை அறிவதற்காகவும், திரவ இரும்புச் சத்து உட்கொண்டோரின் எண்ணிக்கையை அறிவதற்காகவும், எங்கள் ஆய்வுப்பணியாளர்கள் / கிராம சுகாதார செவிலியர் ஒரு சில கேள்விகளை உங்களிடம் கேட்பார்.

உங்களுக்கு ஏதேனும் விளக்கமோ (அ) மேல்விவரங்களோ தேவைப்பட்டால் எங்கள் ஆய்வுக்குழு உறுப்பினர்களையோ (அ) கிராம சுகாதார செவிலியரையோ தயக்கமின்றி அணுகவும்.

சுய விருப்பம்

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்பது முற்றிலும் உங்களது சுய விருப்பம். இதில் பங்கு பெற மறுக்கவும், பங்கு பெற சம்மதித்த பிறகு எந்த நேரத்திலும் உங்கள் குழந்தையின் பங்கேற்பினை விலக்கிக் கொள்ளவும். உங்களுக்கு முழு உரிமை உண்டு.

பாதிப்பு

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்பதினால், சில இரத்தத்துளிகள் பரிசோதனைக்காகத் தருவதைத் தவிர வேறெந்த பாதிப்பும் ஏற்படாது. இரும்புச் சத்து மருந்து உட்கொள்வதன் மூலம் கருப்பு நிற மலக்கழிவு இருக்கும். மேலும் வெறும் வயிற்றில் (வெகு சிலருக்கே) உட்கொள்வதினால் மிகவும் லேசான வயிற்று எரிச்சல், வயிற்றுப்போக்கு ஏற்படலாம் என்று கூறப்படுகிறது. இந்நிகழ்வு மிகமிக அரிதான

ஒன்றாகும். எனினும் இவ்வாறு ஏற்பட்டால் எங்களது கிராம சுகாதார செவிலியரை உடனடியாக அணுகவும். அவர் உரிய ஆலோசனை மற்றும் மருத்துவ கவனிப்பை அளிப்பார் / ஆரம்ப சுகாதார நிலையத்திற்கு பரிந்துரை செய்வார்.

பலன்கள்

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்பதன் மூலம் நீங்கள் அடையும் பயன்கள் பின்வருமாறு.

1. உங்கள் குழந்தையின் இரத்தத்தின் ஹீமோக்ளோபின் அளவு அறியப்படும்.

2. உங்கள் குழந்தைக்கு இரும்புச்சத்து திரவம் முற்றிலும் இலவசமாகத் தொடர்ந்து 100 நாட்களுக்கு வழங்கப்படும்.

மேலும், இந்த ஆய்வின் மூலம் 6 மாதம் முதல் 35 மாதம் வரை உள்ள குழந்தைகளுக்கு தொடர்ந்து 100 நாட்கள் திரவ வடிவ இரும்புச்சத்து மருந்து கொடுப்பதன் மூலம் இரத்த ஹீமோக்ளோபினில் ஏற்படும் மாற்றத்தினை நாங்கள் அறிந்து கொள்ள இயலும்.

ஊக்கத் தொகை

இந்த ஆய்வில் நீங்கள் பங்கேற்பதற்கு எந்த விதமான ஊக்கத்தொகையும் வழங்கப்பட மாட்டாது.

இந்த ஆய்வில் உங்கள் குழந்தை பங்கேற்க நீங்கள் விரும்பினால் குறியிட்ட இடத்தில் உங்களுடைய கையொப்பமோ அல்லது இடது பெருவிரல் முத்திரையோ இடவும்.

ஒப்புதல் படிவம்

மேற் கூறிய ஆய்வில் என் குழந்தையின் / பாதுகாவலில் இருக்கும் குழந்தையின் பங்கேற்பிற்கு நான் வரவேற்கப்பட்டேன். 6 முதல் 35 மாதத்திற்கு உட்பட்ட குழந்தைகளில், திரவ இரும்புச்சத்து மருந்து தொடர்ந்து 100 நாட்கள் கொடுப்பதின் மூலம் இரத்த ஹீமோக்குளோபின் அளவில் ஏற்படும் மாற்றத்தை கண்டு பிடிக்கும் இந்த ஆய்வின் நோக்கம் மற்றும் இதன் செயல் முறை, இதில் பங்கேற்பதினால் ஏற்படக்கூடிய பாதிப்பு, பலன்கள், விளக்கம் அல்லது மேல் விவரங்களுக்கு தொடர்பு கொள்ள வேண்டிய நபர்களின விபரங்கள் எனக்கு தெளிவாக தெரிவிக்கப்பட்டது.

நான் மேலே கண்ட விவரங்களைப் படித்தேன் / மேலே கண்ட விவரங்கள் எனக்கு புரியும் மொழியில் படித்துக் காண்பிக்கப்பட்டது. கேள்விகள் கேட்க எனக்கு சந்தர்ப்பம் அளிக்கப்பட்டது. நான் கேட்ட கேள்விகளுக்கு எனக்கு திருப்தி அளிக்கும் வகையில் பதில்கள் அளிக்கப்பட்டன. இந்த ஆய்வில் என் குழந்தை பங்கேற்க நான் முழுமனதுடன் சுய விருப்பத்தின் பேரில் சம்மதிக்கிறேன். மேலும், இந்த ஆய்விற்குத் தேவைப்படும் இரத்த ஹீமோக்ளோபின் அளவின் மாற்றத்தைக் கண்டறிய இரு முறையும் என் குழந்தையின் / பாதுகாவலில் இருக்கும் குழந்தையின் இரத்த மாதிரிகளை

கொடுக்கவும் சம்மதிக்கிறேன். பங்கு பெற சம்மதித்த பிறகு என் குழந்தையின் / பாதுகாவலில் இருக்கும் குழந்தையின் பங்கேற்பினை எந்த நேரத்திலும் விலக்கிக் கொள்ள எனக்கு முழு உரிமை உண்டு என்பதனையும் விலக்கிக் கொள்வதினால் என் குழந்தையின் / பாதுகாவலில் இருக்கும் குழந்தையின் மருத்துவ கவனிப்பு எந்த விதத்திலும் பாதிக்கப்படாது என்பதனையும் நான் தெளிவாக அறிவேன்.

பெற்றோர் / பாதுகாவலர் பெயர் கையொப்பம் / இடது கை பெருவிரல் முத்திரை

இடம் : தேதி :

பெற்றோர் அல்லது பாதுகாவலர் படிக்காதவராக இருப்பின்

நேர்முக ஆய்வாளரின் கையொப்பம்

சாட்சியின் பெயர் சாட்சியின் கையொப்பம்

இடம் : தேதி :

இப்படிவ நகலை பெற்றுக் கொண்டேன்.

பெற்றோர் / பாதுகாவலர் பெயர் கையொப்பம் / இடது கை பெருவிரல் முத்திரை

இடம் : தேதி :

Appendix 2. Proforma for Hemoglobin Estimation

State..... District..... Village Name.....

PHC Name .....HSC Name.....

S.No	Name	Age	Sex	Date of collection I	Date of Analysis I	OD		Hb gm/dl I	Date of Collection II	Date of analysis II	OD		Hb gm/dl II
						Std	Sample				Std	Sample	

Appendix 3: Data collection format for the study subjects (6th to 36 months), Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Intervention:

I. Identification information **Informant:**

1. ID. No. ☐
2. Name
3. Sex
4. Age (calculated in years and months)
5. Date of birth ☐ ☐ ☐

   Day month year
6. Address
7. General information :

   Type of family

   Total members in the family

   Birth order of the child

   Monthly income of the family ☐

   Annual income of the family ☐

II. Socio-economic status

1.Place of living ☐ (0 - rented; 1-own)

2.Type of house ☐

(1-Kutcha;2-Pucca;3- Mixed;4- Bungalow)

3. Religion: (1-Hindu;2-Christian;3-Muslim;4-Others)

4. Caste: (1-SC;2-ST;3-BC;4-MBC ;5-Others)

5. Parents Qualification

Mother ☐ Father ☐

(0-No education;1-Primary;2-Middle; 3 - High school level, 4 - Higher secondary school level, 5 - Graduate level, 6 - Post graduate level (Arts, Commerce, Science), 7 - Professional/Technical etc.) ☐

6. Highest education in the family

(0 - No education, 1 - Primary level, 2 - Middle level, 3 - High school level,

4 - Higher secondary school level, 5 - Graduate level, 6 - Post graduate level (Arts, Commerce, Science), 7 - Professional/Technical etc.)

7. Occupation of parents:

Father:

Mother: ☐

8. Highest occupation in the family

(0-Presently not employed gainfully, 1-Labour, unskilled, 2-Labour skilled, 3-Small business, 4-Independent profession, 5-Cultivator owner/ tenant / Land owner, 6-Service: govt./private/ex. Service)

9. Material possessions

(1-Tape recorder; 2-TV, 3- Refrigerator, 4-Washing machine ; 5-Two wheeler,

6-VCP/VCD;7-Four wheeler, 8-Computer,9- Air conditioner, 10- Others)

1II. Birth details

1. Where did the delivery take place?
2. Was it full term?
3. Where there any complications? If yes, details
4. What was the birth weight of the baby? ☐
5. Was breast feeding started? If yes, when?

IV. Personal history

1. Did you immunise your child according to the schedule?(1-Yes ,2-No)

2.If yes , please show the card(Note down the details)

Vaccine	Date/Month
Zero polio	
BCG	
DPT I	
DPT II	
DPT III	
Polio I	
Polio II	
Polio III	
Measles	
DT Booster	
Pulse polio	Doses-

3. Mile stone development according to age

Age at which head fixed

Age at which the child sat without support

Age at which the child walked without support

Age at which the child talked

4. Does your child fall sick often? ☐

(1- yes, 2-no)

5. If yes , how often?

6. What are the common diseases that affect your child?

7. Do you get any treatment? (1-yes, 2-no) ☐

8. If yes, from where do you get treatment?

9. If no, what do you do?

10. Does your child has the habit of anal scratching? (1-yes, 2-no) ☐

11. Does your child has the habit of eating soil, viboothi etc..,

(1-yes, 2-no) ☐

12. Have you ever noticed worms in your child's feces? (1-yes, 2-no) ☐

13. If yes, what did you do about it?

V. Dietary history of the child

1. Do you breast feed your child now? ☐

(1-Yes;2-No)

2. If yes, how often do you breast feed in a day?

3. Do you give any additional food to your child?(1-Yes;2-No) ☐

4. If yes, please provide details (diet/day)

5.What type of food does your child eat? ☐

(1-Vegetarian, 2-Non-vegetarian)

6. If non-vegetarian how often does your child eat non-vegetarian food? ☐

(1-Once weekly,2-Once fortnightly,3-Once Monthly,4-Others specify)

7. How often does your child take green leafy vegetables? ☐

(1- daily,2-twice weekly, 3- Once weekly,4-Once fortnightly,

5 -Once Monthly, 6-Others specify

8.How often does your child take fruits? ☐

(1- daily,2-twice weekly, 3- Once weekly,4-Once fortnightly,

5 -Once Monthly, 6-Others specify

Signature of the interviewer Date

Appendix 4. General examination of the study subjects, Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003.....

Intervention:

I. Identification information **Informant:**

1. ID. No. ☐
2. Name
3. Sex
4. Age (calculated in years and months)
5. Date of birth ☐ ☐ ☐

   Day month year
6. Address

II. General examination

1.Stature	2. Built	3.Skin
4.Hair	5.Abdomen	6.Pedal edema
7.Pallor	8.Koilonychia	9.Web spaces

III. Physical examination

Height (in cms)	Weight (in kg)
Pulse	CVS
RS	Abdomen

IV. Check the growth chart card(if present); note the details

V. Medical History

a. H/O chronic illness
b. H/O medication
c. Drug allergy

Signature of the examiner Date

Appendix 5. Follow up of the study subjects Thimmavaram Health Sub Centre, Saidapet Health Unit District, Tamilnadu, 2003

Times of visit	Date of visit	No. of days Of drug intake	Cumula -tive total days of drug intake	Reasons for non compliance	Sign of investi -gator	Sign of Super- visor
September 2003						
I						
II						
October 2003						
I						
II						
III						
IV						
V						

November 2003						
I						
II						
III						
IV						
V						
December 2003						
I						
II						
III						
IV						
V						

Remarks if any

Appendix 6. Compliance Card

திரவ இரும்புச் சத்து மருந்து வழங்கப்பட்ட விபர அட்டை

குழந்தையின் பெயர் : வயது :

பெற்றோர் பெயர் : கிராமத்தின் பெயர் :

மாதங்கள்	மருந்து வழங்கப்பட்ட தேதிகள்															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
செப்டம்பர் 03																
அக்டோபர்																
நவம்பர்																
டிசம்பர்																
ஜனவரி 04																

ாதங்கள்	மருந்து வழங்கப்பட்ட தேதிகள்															
	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	
ச்டம்பர் 03																
க்டோபர்																
வம்பர்																
ம்பர்																
னவரி 04																

பற்றோர் / காப்பாளர் கையொப்பம் :

ூராய்ச்சியாளரின் கையொப்பம் : தேதி :

Appendix 7. Definitions for selected Socio-economic variables:

1. Type of house:

Hut: usually one room-construction of mud walls with a thatched roof.

Kutcha: construction with more than one room with mud walls and a thatched roof.

Mixed: A house, which has one or two of the following. Cement or mortar used for plastering of wall of floor with the tiled roof.

Pucca: One which is built with a foundation, using stone or bricks with mortar and cement and having a concrete or stone laid roof or tiled roof.

Mansion: A large house containing more than 5 rooms (excluding kitchen and roof)

2. Occupation:

Presently not gainfully employed:
Housewife, Household work, Retired, Student, Preschool, Unemployed

Labour unskilled / Agricultural:
Those who are engaged by others on wages. Usually they get wages on daily basis and maintain their households with wages. e.g., Landless labourer, manual labourer, cleaner, server, domestic work, construction work, watchman

Skilled labourer:

Include artisans who follow their caste. Occupations like tailor, blacksmith, goldsmith, carpenter, washer man, potter, barber, electrician, dhobi, shepherd, basket weaving, masonry, mechanic, driver and beedi workers can be included.

Small business:

Traders who maintain petty shops and are engaged in small business and trade activities.

Independent profession:

High-prestige but low income jobs; includes persons who are in employment not carrying high social status. In this will be included the "class IV employees" and village level workers.Traditional birth attendant, peon, ayah, attender, balwadi teacher, community nutrition worker and temple priest.

Land owner/ Cultivator owner / Cultivator tenant:
Landowner:
A person who owns land and cultivates it himself. In addition, may hire other people to work on.

Cultivator owner:

A person who owns land and cultivates it himself. In addition, he/she may hire other people to work on his/ her land.

Cultivator tenant:

The land is leased from someone else and he cultivates it. He may also hire other people to work.

Service:

The highest social status is for professions like medical, legal and engineering professions and for employment involving administrative responsibilities. In this category, people like headmasters; officers in government (police, armed forces) and other employment (business man, factory owner), supervisory personnel etc will be included.

Appendix 8. Methods used for measuring Socio-Economic Status

Socio-economic Score (SES)

SES was constructed by combining the socio-economic variables like place of living, type of house , education of the mother and occupation of the father.

Indicators for Socio-Economic Status

1.Place of living ☐ (0 - rented; 1-own)

2.Type of house ☐ (1-Kutcha;2-Pucca;3- Mixed;4- Bungalow)

3. Education of the mother ☐

(0-No education;1-Primary;2-Middle; 3 - High school level, 4 - Higher secondary school level, 5 - Graduate level, 6 - Post graduate level (Arts, Commerce, Science), 7 - Professional/Technical etc.)

4. Occupation of father ☐

(0-Presently not employed gainfully, 1-Labour, unskilled, 2-Labour skilled, 3-Small business, 4-Independent profession, 5-Cultivator owner/ tenant / Land owner, 6-Service: govt./private/ex. Service)

Socio-economic score was constructed using above-mentioned variables. Socio economic score = Total of scores on the four indicators mentioned above.

Iron and folic acid group : The maximum and minimum scores were 14 and 2. The scores were then grouped into low, medium and high socio-economic groups by dividing at the 33 percentile. The percent of low, medium and high socio-economic group was 36.5, 35.7and 28.0respectively.

Iron alone group: The maximum and minimum scores were 12 and 2. The scores were then grouped into low, medium and high socio-economic groups by dividing at the 33 percentile. The percent of low, medium and high socio-economic group was 37.0, 40.2and 22.8respectively.

Appendix 9.
Abbreviations

AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
DDHS	Deputy Director of Health Services
E. Med	Eastern Meditteranean
FETP	Field Epidemiology Training Programme
HSC	Health Sub Centre
HUD	Health Unit District
ICDS	Integrated Child Development Scheme
ICMR	Indian Council of Medical Research
IDA	Iron Deficiency Anemia
INACG	International Nutritional Anemia Consultative Group
IFA	Iron with Folic acid
IPC	Iron III Hydroxide Polymaltose Complex
LBW	Low Birth Weight
MAE	Mater of Applied Epidemiology
MRP	Maximum Retail Price
NFHS	National Family Health Survey
NIE	National Institute of Epidemiology
NIN	National Institute of Nutrition
NNACP	National Nutritional Anemia Control Programme
NNAPP	National Nutritional Anemia Prophylaxis Programme
NNMB	National Nutrition Monitoring Bureau
OMNI	Opportunities for Micronutrient Interventions
PHC	Primary Health Centre
SD	Standard Deviation
SEA	South East Asia
UNICEF	United Nations Children's Fund
UK	United Kingdom
USAID	US Agency for International development
W. Pacific	Western Pacific
WHO	World Health Organisation