Efficacy of Sodium Iron EDTA in the Fortification Programs

Iron fortificants

WATER SOLUBLE COMPOUNDS

Dissolve instantaneously

ferrous sulfate
ferrous gluconate
RBV = 100

Ferrous bisglycinate
Sodium iron EDTA

POORLY WATER SOLUBLE /SOLUBLE IN DILUTE ACID

Dissolve completely over time

Ferrous fumarate
Ferrous succinate

COMPOUNDS WATER INSOLUBLE/POORLY SOLUBLE IN DILUTE ACID

never dissolve completely

Elemental iron:
Electrolytic
Carbonyl
Reduced
Ferric pyrophosphate
Ferric orthophosphate

Hurrell, 2007

Relative Bioavailability of iron compounds

Iron Fortificants	RBV
Ferrous sulfate Encaps. ferrous sulfate Ferrous fumarate Encaps. ferrous fumarate	100
Elemental iron Electrolytic Carbonyl H-reduced Ferric pyrophosphate	 13-148 5 – 20 13-148 21-74
NaFeEDTA Ferrous bisglycinate	100-390 90-350

WHO, 2006

NaFeEDTA

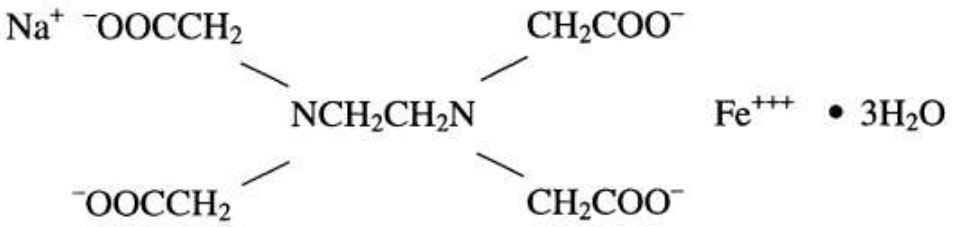


Fig. 1. Sodium iron ethylenediaminetetraacetic acid (NaFeEDTA).

Ferric iron generally poorly absorbed

→ Use of EDTA as a chelator

EDTA binds Fe in soluble complex → Fe can't bind to phytate, inhibitors or hydroxyl ions

Duodenum : Fe released from EDTA absorbed by normal physiological mechanisms

Candela et al., 1984

Heimbach et al., 1999

Hurrell, 2002

NaFeEDTA – Molar Ratio

Type of Meal	Molar ratio	Effect on Fe absorption	Source
Complementary Chinese food	EDTA:Fe 0.7:1 EDTA:Fe 0.4:1	No increase Increase	Chang et al., 2012
Margarine in women	14 mg added Fe as MGFePP or NaFeEDTA	Body iron stores increase 2-3 times with NaFeEDTA	Andersson et al., 2010
Wheat	EDTA:Fe 0.067:1	Maximum increase	Hurrell et al., 2002
High-phytate wheat-soy cereal	EDTA:Fe 1:1	Maximum increase	Hurrell et al., 2002
Rice fortified with $FeSO_4$	EDTA:Fe 0.5:1	Maximum increase	MacPhail et al., 1994

Fe absorption increases with NaFeEDTA compared to FeSO4 or ferrous fumarate

Hurrell, et al., 2000

Effect on other minerals

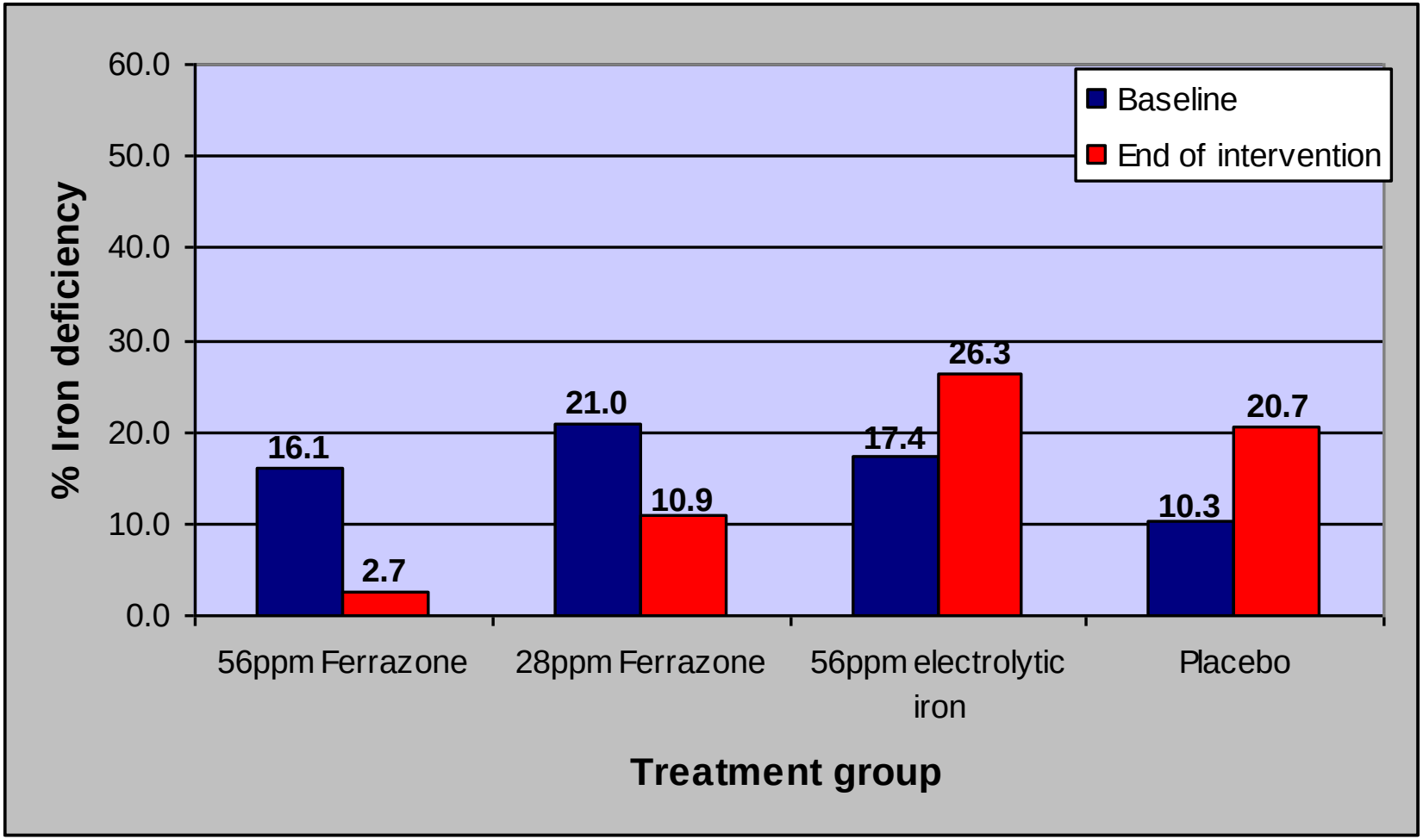
Study population	Mineral	Effect of NaFeEDTA compared with $FeSO_4$	Effect of NaFeEDTA compared with $FeSO_4$ and Ascorbic acid
Women, wheat-based meal (Davidsson et al., 1994)	**Zn**	Significant increase	NA
	Ca	No change	NA
Adult, weaning cereal (Davidsson et al, 1998)	**Mn**	No change	NA
Infant, complementary food (Davidsson et al., 2005)	**Zn**	NA	No change
	Cu	NA	No change
	Ca	NA	No change
	Mg	NA	No change

Safety

Concerns	Explanations	Source
Fe overload	No risk if 0.2 mg FE/kg body weight	JECFA, 2000; CanTox, 2003
Fe Toxicity in children	Fe toxicity : 25 mg Fe/kg body weight Fe poisoning : 60 mg/kg body weight	Whittaker et al., 2002
Interferences with minerals	Rats studies show no adverse effect	Garby and Areekul, 1974, Soalomons et al., 1979, Viteri et al., 1995
Mutagenecity	Mouse lymphoma TK : no difference with other Fe compounds	Dukel et al., 1999
EDTA toxicity	**Pigs** : 72-91% of Fe and EDTA found in feces **Rats** : minimal difference with ferrous sulfate **Human** : 1% Fe intact Fe	Candela et al., 1984 Appel et al., 2002 MacPhail et al., 1981

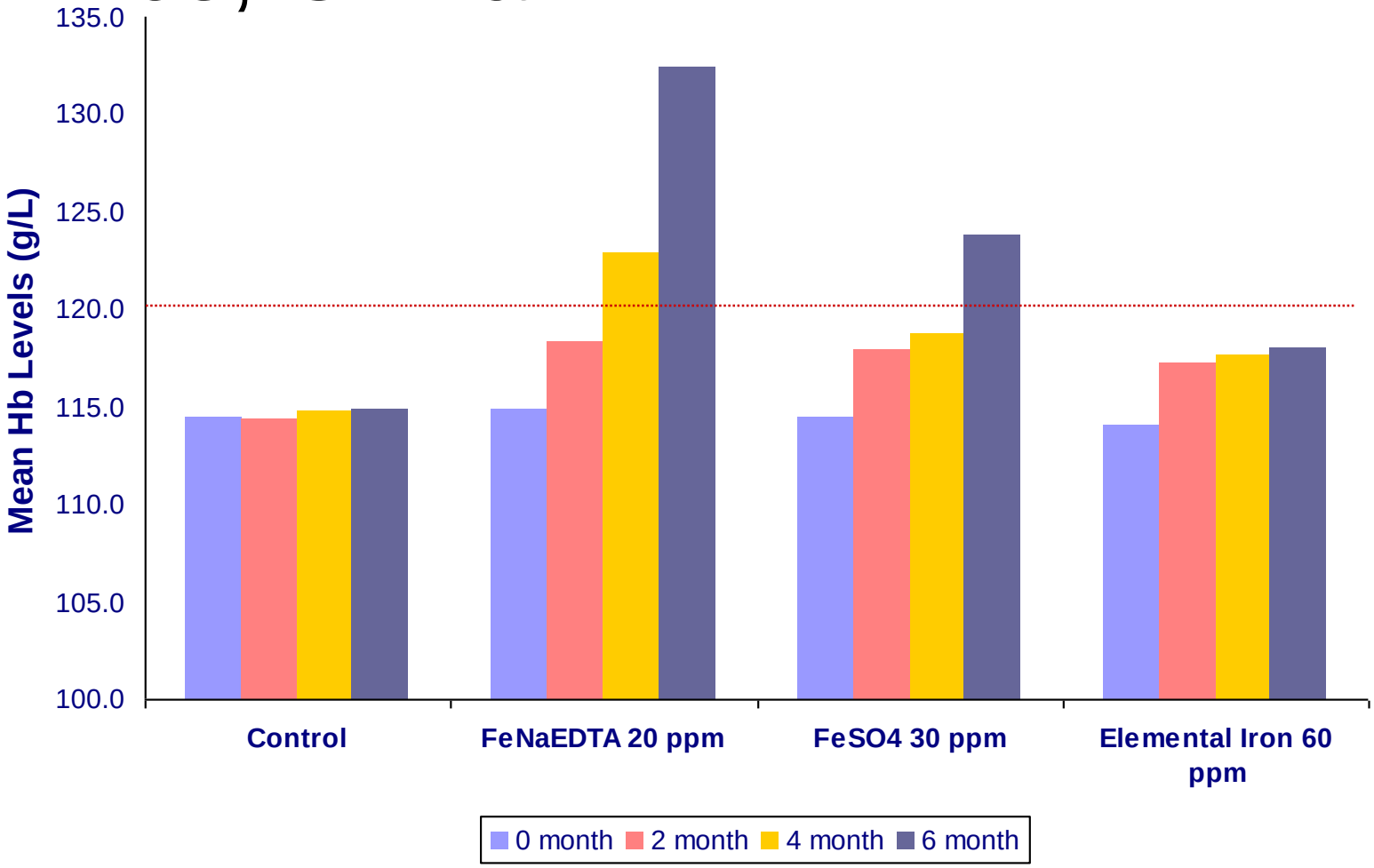
Atta wheat flour intake (g/d)	Iron from NaFeEDTA added to flour (mg/kg)	Dietary iron delivered from NaFeEDTA (mg/d)	Physiological iron from NaFeEDTA (10%) (mg/d)	Price to deliver NaFeEDTA (Rs/MT)
100	31	3.1	0.31	*149*
100	31	3.1	0.16	*37*

Impact maize fortification with NaFeEDTA on prevalence of ID in Kenyan school children



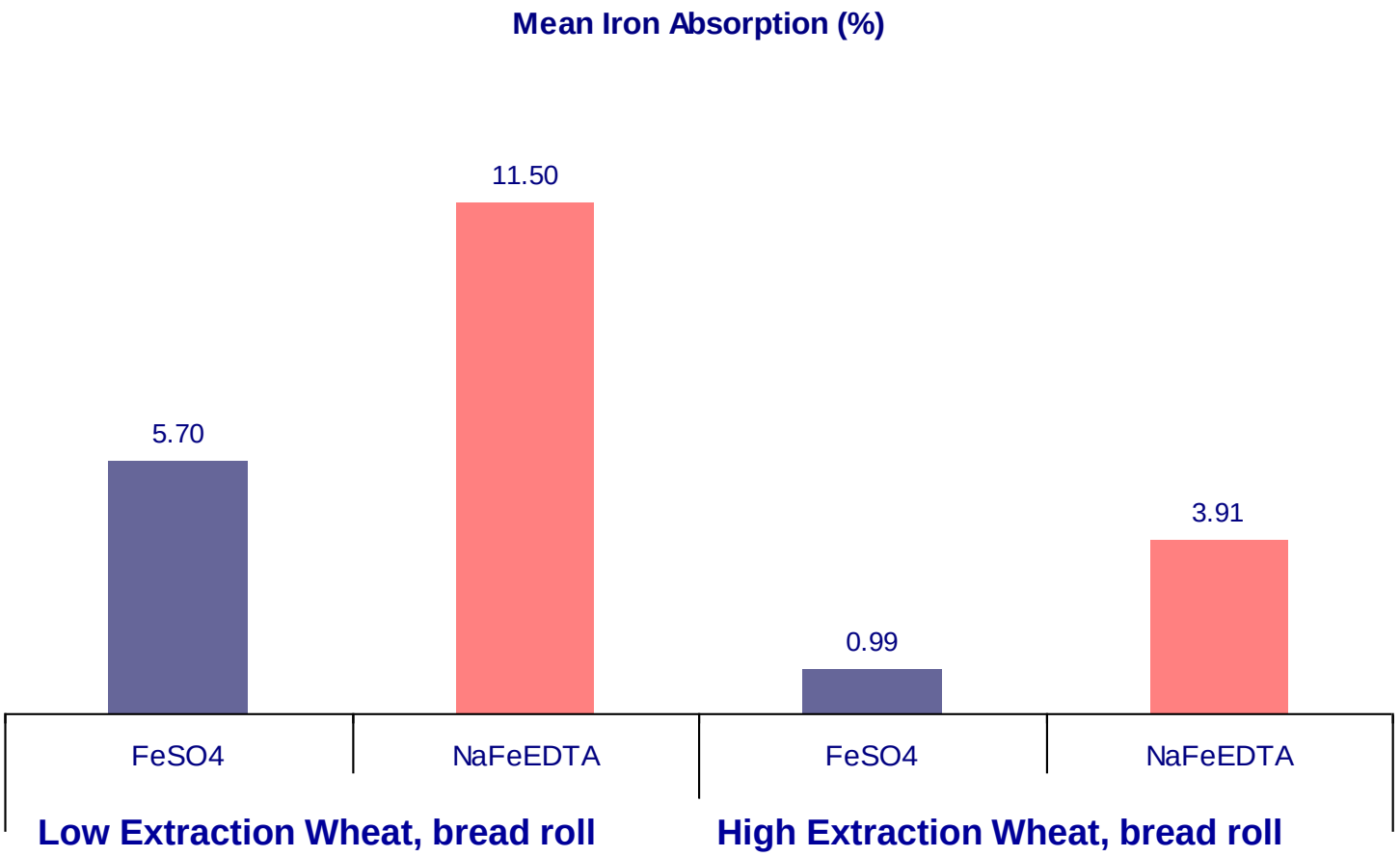
Andang'o *et al*. (2007)

Impact on prevalence of anemia with iron-fortified wheat flour in Henan Province, China



Chen Chunming *et al.* (2005)

Iron Absorption from Cereal Foods



Hurrell *et al.* (2000)

Objectives

1. To test the efficacy of NaFeEDTA fortified wheat flour in reducing the prevalence of anemia and iron deficiency and in improving iron status and total body iron in Indian school children

2. To assess the effect of NaFeEDTA fortified wheat meal on the cognitive performance of school children

3. To evaluate NaFeEDTA fortified wheat flour in organoleptic studies in India

Study sites & Investigators

- Urban school- Bangalore City – AV Kurpad
- Rural Schools, Vadu, Pune – CS Yajnik

Ethical approval

- The study protocol was approved by the Ethical committees of
  - St. Johns Medical College, Bangalore, India
  - KEM Hospital, Pune

- Informed, written consent obtained from parents

  Oral assent obtained from children

Flour preparation & mixing

Flour:

Whole wheat flour from Christy Industries, Tiruchengodu, Tamil Nadu

Iron fortificant:

NaFeEDTA (Ferrazone), Akzo Nobel Functional Chemicals

Mixing at the factory:

2 metric tons mixed @ 6 mg NaFeEDTA in 100 g of wheat flour (July 2007 and December 2007)

The mixed flour was packed in colour coded 20 kg bags and stored at room temperature

Baseline Screening

1317 children screened

Indicators

- Five ml of whole blood by venipuncture
  - Hemoglobin (Hb)
  - Serum ferritin (SF)
  - Zinc protoporphyrin (ZnPP)
  - Serum transferrin receptor (TfR)
  - C-reactive protein (CRP)

Inclusion criteria

Iron deficiency with or without anemia defined as:

SF <15 µg/L or
and/or TfR >7.6 mg/L

Subjects and study design

- 7-mo, randomized, double-blind, controlled trial
- 6 mg of Fe (as NaFeEDTA) / 100 g of local high extraction whole wheat flour as a lunch meal, 6 days a week

401 Fe-deficient children
6-13 year olds

200 children
(NaFeEDTA flour)

201 children
(Control flour)

- Iron status assessed at 3.5 and 7 months after start of intervention

Baseline Characteristics

Parameters	*Iron group N = 97*	*Control group N = 97*
Age (y)	10.4 ± 2.5	10.2 ± 2.7
Weight (kg)	26.2 ± 7.9	25.3 ± 7.8
Height (m)	1.32 ± 0.14	1.30 ± 0.15
Hemoglobin (g/dL)	12.6 ± 1.3	12.7 ± 1.2
Serum Ferritin[1] (µg/L)	12.9 (6.9, 24.3)	12.8 (7.4, 22.2)
Transferrin Receptor (mg/L)	6.5 ± 4.2	6.4 ± 3.0
Total body iron (mg/kg)	1.2 ± 2.9	1.3 ± 2.7

[1]Geometric mean (mean -1SD, mean +SD)
No significant differences between groups

Changes over time - Anthropometry

	n	Time		
		Baseline	**3.5 mo**	**7 mo**
Body weight, *kg*				
Treatment group	182	27.0 ± 8.1	29.2 ± 9.0	30.2 ± 9.3
Control group	180	26.0 ± 7.1	28.1 ± 8.8	29.3 ± 9.2
Height, *m*				
Treatment group	172	1.34 ± 0.15	1.36 ± 0.14	1.38 ± 0.14
Control group	180	1.32 ± 0.15	1.35 ± 0.15	1.37 ± 0.15

Change in anthropometry and iron status over 7 months

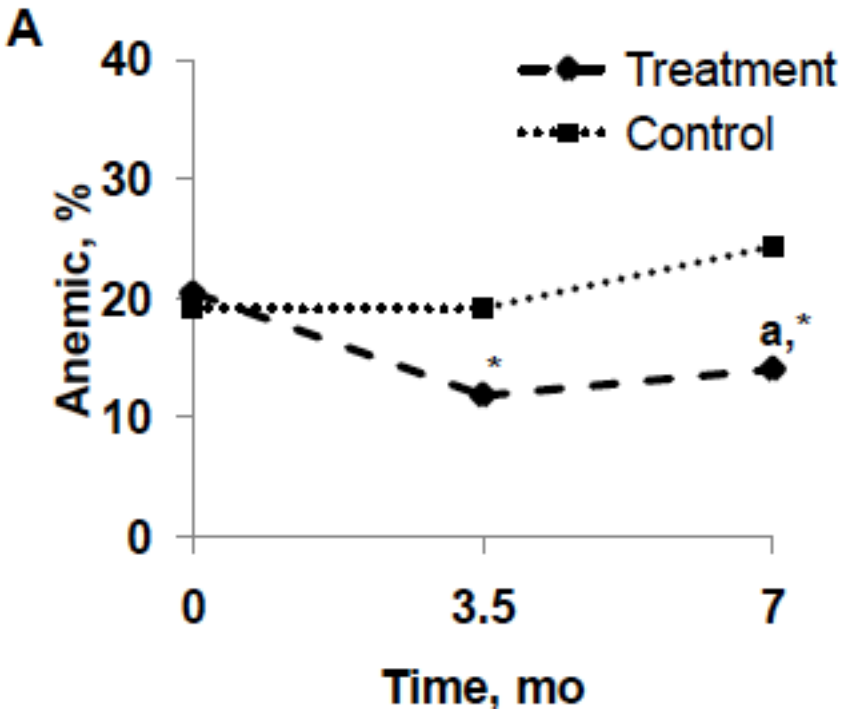
	0 months		3.5 months		7 months	
	Iron group	**Control group**	**Iron group**	**Control group**	**Iron group**	**Control group**
Weight (kg)	**26.2 ± 7.9**	**25.3 ± 7.8**	**28.0 ± 8.7**	**26.4 ± 8.2**	**29.3 ± 9.1**	**27.8 ± 8.7**
Height (m)	**1.31 ± 0.13**	**1.30 ± 0.14**	**1.34 ± 0.14**	**1.32 ± 0.15**	**1.36 ± 0.14**	**1.34 ± 0.15**
Hb (g/dl)	**12.6 ± 1.2**	**12.7 ± 1.2**	**12.9 ± 1.0**	**12.5 ± 1.3**	**13.3 ± 1.1****†**	**12.7 ± 1.4**
SF [1](µg/l)	**12.5 (6.6, 23.3)**	**12.7 (7.2, 22.2)**	**19.1 (9.8, 37.3)**	**13.6 (6.7, 27.7)**	**24.8****†** **(13.6, 45.2)**	**13.1 (6.7, 26.0)**
sTFR (mg/l)	**6.5 ± 4.2**	**6.4 ± 3.1**	**6.5 ± 4.2**	**6.9 ± 2.5**	**6.4 ± 2.2******	**7.6 ± 3.4**
Total body iron (mgkg)	**1.2 ± 2.9**	**1.3 ± 2.7**	**2.8 ± 2.9**	**1.2 ± 3.3**	**3.6 ± 2.7****†**	**0.7 ± 3.3**

[1] Geomean (mean- SD, mean +SD)

**** Significantly different between each other; † significantly different from baseline P<0.01**

Hb, SF, sTfR, and TBI: significant *time x treatment* interaction (P<0.05)

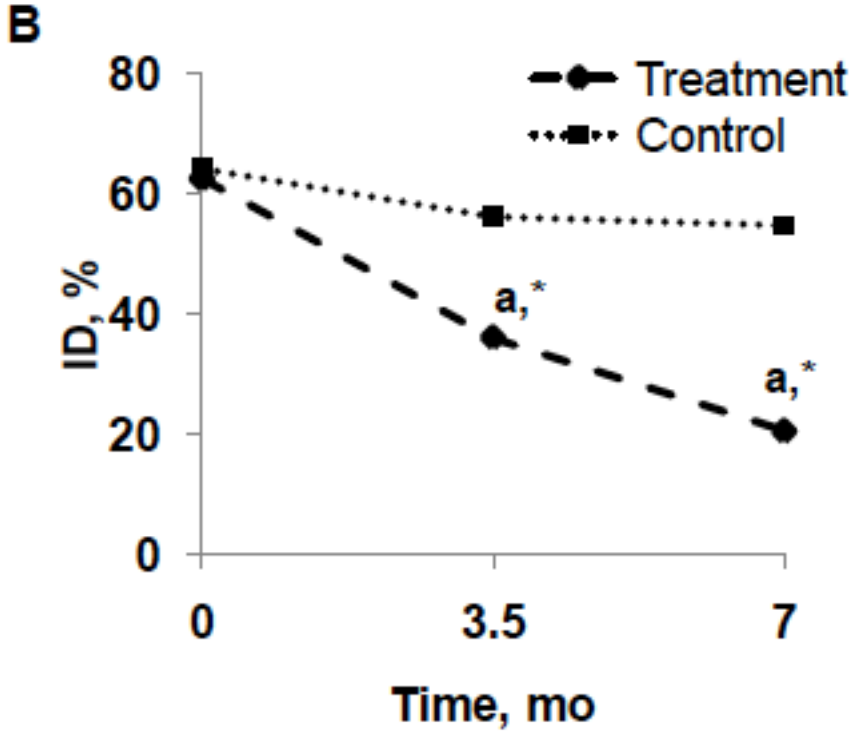
Change in Anemia Prevalence

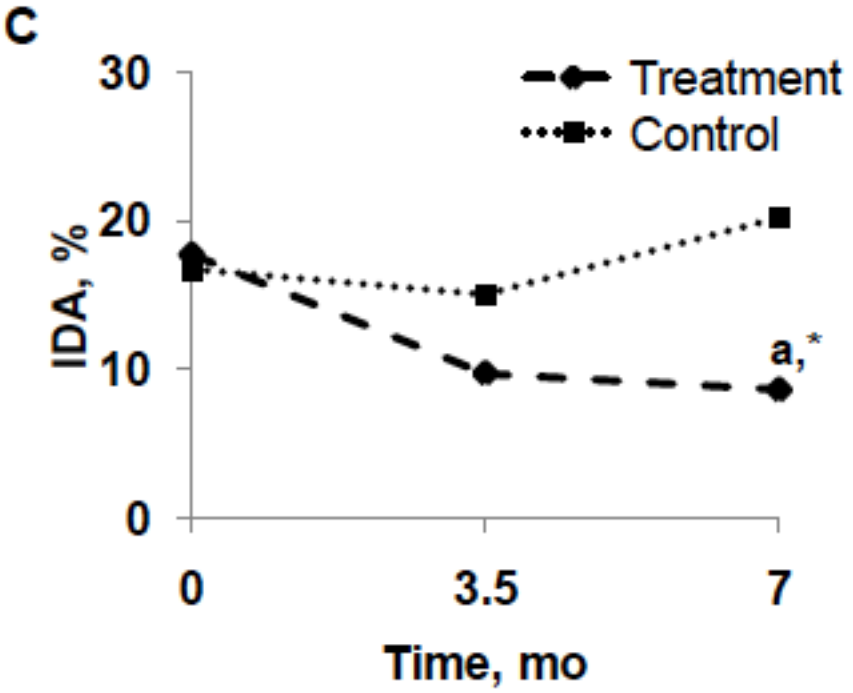


Anemia prevalence decreased from 18% to 7% in the fortified group

Time x treat – $p<0.01$

Change in ID and IDA prevalence





Organoleptic Testing

Triangle Test

- 3 different common meals prepared using the NAFeEDTA flour and the control flour by a local cook using traditional recipes
- A panel of 20 local women
- Three coded samples of the each food will be given in random order

Instructions:

Assess flavor, odor and color of local dishes

Determine the one that is different and describe how it differs

Triangle tests for sensory assessment

Food tested	No of Subjects (N)	No of correct answers (N)	Significance
Raw wheat flour (6 mg/100g)	18	4	NS
Raw wheat flour (10 mg/100g)	18	4	NS
Wheat chapathi (6 mg/100g)	18	6	NS
Wheat chapathi (10 mg/100g)	18	5	NS
Wheat poori (6 mg/100g)	18	2	NS
Wheat poori (10 mg/100g)	18	4	NS
Wheat dosa (6 mg/100g)	18	4	NS
Wheat dosa (10 mg/100g)	18	6	NS

Conclusions

- Whole wheat flour fortified with NaFeEDTA is efficacious in reducing IDA and ID prevalence and improving iron status and body iron stores in iron deficient school Indian children
- NaFeEDTA is an ideal iron compound for whole wheat flour fortification
- Strong evidence base for action - Mass fortification for use in school meal programs and in PDS must be considered