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A comparative study between the dispersible Ferric pyrophosphate particles and Ferrous sulfate in treatment of pediatric patients with iron deficiency anemia

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Abstract
Background: Iron deficiency anemia (IDA) is the most common type of anemia related to malnutrition worldwide. It represents a major problem in developing countries, especially in Egypt. Ferric pyrophosphate (FPP) is a water-insoluble iron compound often used to fortify infant cereals and chocolate drink powders. It causes no adverse color and flavor changes to food vehicles. This study was done to compare the efficacy of FPP (micro dispersed iron) and ferrous sulfate (FS) in treating childhood IDA.
Materials and Methods: This prospective cohort study was conducted on 58 anemic children visiting the outpatient clinic, pediatric department of Menoufia University hospitals from March 2017 to June 2019. The inclusion criteria of the involved children were age 2 - 12 years and the diagnosis of IDA. Patients with other types of anemia were excluded from the study. Verbal permission was obtained from the parents of the children according to the ethical committee of Menoufia University. Patients were randomly divided into 2 groups. Group1 included 29 children who were treated with FPP and group2 included 29 children who were treated with oral traditional iron in the form of FS. Complete blood count and iron profile were recorded before and after 8 weeks of treatment.
Results: The results showed no statistically significant difference between the FPP group and the FS group regarding clinical examinations (P-value > 0.05). There was no significant difference regarding hemoglobin, serum iron, and serum ferritin between the FPP and the FS groups after treatment (P-value> 0.05). However, side effects were significantly higher in the FS group (P-value > 0.001).
Conclusion: Micro dispersed iron could be used as an alternative therapy for children with IDA who refuse oral iron therapy in a liquid form with more tolerability and fewer side effects.
Key words: Ferric pyrophosphate, Ferrous sulphate, Iron deficiency anemia

Introduction

The definition of iron deficiency anemia (IDA) is defined as the hemoglobin (Hb) level below the 5th percentile of normal for the age that is caused by lack of iron. Most studies showed that the cut-off point of Hb for IDA is around 11g/dL (-2 standard deviation below the mean) (1). IDA is the most common type of anemia related to malnutrition worldwide. It represents a major problem in developing countries, especially in Egypt (2). The causes of IDA are decreased iron intake, chronic bleeding, or both of them (3). Complications of IDA are decreased physical activity, impaired cognition and immunity, and delay psychomotor development (4). There are many laboratory tests for diagnosis of IDA with poor sensitivity and specificity because they are modified by other conditions such as inflammation instead of iron deficiency. So, combining several iron status indicators provides the best assessment of iron status (5).

Treatment of IDA consists of treating the cause and restoration of normal levels of red blood cells (RBCs), Hb, and iron stores (6). Providing adequate iron supplementation to prevent IDA development is also important to prevent neurological and developmental complications in infancy and childhood (7). Long-term oral iron is frequently used as first-line therapy, but iron salts such as ferrous sulfate (FS) are frequently

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associated with a high incidence of gastrointestinal side effects such as nausea, vomiting, diarrhea, and constipation. They may cause discontinuation of treatment (8). Ferric pyrophosphate (FPP) or micro dispersed iron) is a water-insoluble iron compound often used to fortify infant cereals and chocolate drink powders. Its main advantage is that it causes no adverse color and flavor changes to food vehicles (9). Using microemulsion dispersion technique based on the ferric form of iron results in micronized, dispersible FPP particles of very small average size (approximately 0.3mm) that has been reported to have a similar bioavailability to FS (10). The issue of efficacy between these two therapies remains unsettled. This study was planned to clarify this issue and confirm whether there was any significant difference between the efficacy of FS and FPP.

Materials and Methods

Ethical statement

This research was performed under the Declaration of Helsinki. Informed consent was received from all parents of patients or patients before beginning the study. The research was approved by the ethics committee of the faculty of medicine, Menoufia University with the approval code of 4-2018PED2**.** This prospective cohort study was carried out on 58 children who were diagnosed with IDA, visiting the outpatient clinic, pediatric department of Menoufia University hospitals from March 2017 to June 2019. Inclusion criteria were children with IDA aged 2-12 years old with the following laboratory data before starting the treatment (Hb <11g/dl, mean corpuscular volume (MCV) <70 fl, red cell distribution width (RDW) >16%, serum ferritin <12 ng/ml, serum iron <40 µg/dl, total iron-binding capacity (TIBC) >400 µg/dl, transferrin saturation (TSAT)<10% (**11).** Exclusion criteria included children with any other types of anemias and children less than 2 years and more than 12 years.

Group 1 Included 29 pediatric patients with IDA who were treated with oral micronized dispersed iron in the form of a 350gm jar of liquid chocolate. At the dose of 7.5mg twice a day to children below 4 years old and 15mg twice a day to children above 4 years old for 2 months (Manufactured by Devart Lab pharmaceuticals® Egypt)

Group 2 included 29 pediatric patients with IDA who were treated with oral traditional iron in the form of FS (50mg /5ml solution) at the dose of 6mg/kg/day for two months (**12).**

All children included in the study were subjected to the following issues.

1- **Full history taking**: pica, easy fatigability, lethargy and shortness of breath, impaired scholastic performance, loss of concentration, and headache
2- **Thorough clinical examination with the emphasis on**: -
   - General examination including vital signs: tachycardia, pallor, and repeated infection
   - Central nervous system (CNS) examination: loss of concentration
   - Cardiovascular system examination: tachycardia and functional systolic murmur
   - Abdominal examination
3- **Anthropometric Measurements:** Weight, height, and calculation of body mass index (BMI).

Laboratory evaluation in the form of:

- Complete blood count (CBC) (using automated system XN-10 hematology analyzer)
- Iron profile: serum iron (normal value: 50-120µg/dl) and total iron-binding capacity (normal value 240-450µg/dl) (using Cobas Integra 400 plus analyzer)
- Serum ferritin (normal value: 12-300 ng/ml) (using electrochemiluminescence immunoassay on Cobas e411 immunoassay analyzer)
- The percentage of TSAT (normal value: 20-50%)

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Statistical method: Data were obtained on weeks 0 and 8 and was entered on a pre-designed proforma for each patient. SPSS-10.0 was used for statistical analysis **(13).** Mean and standard deviation were calculated for the result obtained before and after two-month treatment. The efficacy between two groups was compared by the chi-square test. It was applied to compare different data. P-value ≤ 0.05 was accepted as significant.

Results

The results showed that in the FPP group, male children were 41.4%, while female children were 58.6%. In the FS group, male children were 24.1% and female children were 75.9%. Both groups were comparable base on sex and age with no statistically significant difference (P-value > 0.05) (Table (I)).

The result showed that there was no statistically significant difference regarding weight, height, BMI, general condition, CVS, CNS, and abdominal complaints between both groups before treatment (P-value > 0.05). Regarding laboratory findings, the results showed that there was no statistically significant difference regarding RBCs count, Hb, MCV, mean corpuscular hemoglobin (MCH), hematocrit (HCT), RDW, white blood cells (WBCs) count, platelet count, serum iron, serum ferritin, TSAT and TIBC between both groups before treatment (P-value > 0.05).

After two-month treatment, the results showed that there was no statistically significant difference between the FPP and the FS groups regarding weight, height, BMI, general condition, CVS, CNS, and abdominal complaint (P-value > 0.05). Regarding laboratory findings, the results showed that MCV, MCH, HCT, and TSAT were significantly lower in the FPP than the FS group (P-value < 0.05). TIBC was significantly higher in the FPP than the FS group (P-value < 0.05). While, the results showed that there was no significant difference regarding Hb, RDW, RBCs count, platelet count, serum iron, and serum ferritin between the FPP and the FS group after treatment (P-value > 0.05).

Side effects were significantly lower in the FPP than the FS group after two-month treatment (P-value ≤ 0.001). Constipation, gastric upset, and abdominal cramps were significantly lower in the FPP than the FS group (P-value < 0.05), while there was no significant difference between both groups regarding vomiting and black stool (P-value ≥ 0.05).

The results showed that weight, BMI, general condition, CVS, and CNS complaint were significantly improved in group 1 after two-month treatment with micronized dispersed iron (P-value < 0.05). Also, the results showed that RBCs count, Hb, MCV, MCH, HCT, serum iron, serum ferritin, and TSAT were significantly higher (P-value < 0.05), WBCs count, platelet count, and RDW were significantly lower (P-value < 0.05) in group 1 after two-month treatment with micro dispersed iron, while there was no significant difference regarding TIBC after treatment (P-value > 0.05).

The results showed that weight, height, BMI, general, CVS, and CNS complain were significantly higher in group 2 after two-month treatment with the traditional oral iron (the FS) (P-value < 0.05). Also, the results showed that RBCs count, Hb, MCV, MCH, HCT, serum iron, serum ferritin, TSAT, and TIBC were significantly higher (P-value < 0.05), while RDW was significantly lower (P-value < 0.05) after two-month treatment with FS. Also, the results showed that there was no significant difference regarding WBCs in group 2 after two-month treatment with the traditional oral iron.

Table I: Demographic characteristics of the studied groups.

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	Group (1) (n=29)	Group (2) (n=29)	Test of significance	P-value
Sex			*= 1.957	0.162
Males	12 (41.4%)	7 (24.1%)		
Females	17 (58.6%)	22 (75.9%)		
Age (years)			** = 0.444	0.657
Range (min.-max.)	3-10.4	2-11		
Mean ± SD	5.7±2.01	5.8±3.07		

n= patient number, * **X2**:- Pearson chi square , ** **U** :- Mann-Whitney test , Min-max: minimum to maximum **SD**= standard deviation , **P-value**:- Non-significant (P-value ≥ 0.05), Significant (P-value < 0.05), Highly significant (P-value ≤ 0.001). Group (1) was treated by micronized dispersed iron, Group (2) was treated by oral traditional iron

Table II: Comparison of the clinical examination and laboratory investigation results between group (1) and group (2) before treatment.

	Pre - treatment		Test of significance X^2	P-value
	Group (1) (n=29)	Group (2) (n=29)		
Weight(kg)			*	0.293
- **Range**	12-35	9-48	1.052	
- **Mean ± SD**	19.2±6.5	20.48±12.5		
Height(cm)			*	0.691
- **Range**	90-134	80-138	0.397	
- **Mean ± SD**	108.1±3.03	106.3±20.03		
BMI			*	0.489
- **Range**	12.98-20.3	12.49-25.2	0.693	
- **Mean ± SD**	16.07±2.05	16.3±3.8		
General:			**	0.68
- **Good general condition**	13 (44.8%)	10 (34.5%)	0.78	
- **Pallor**	10 (34.5%)	13 (44.8%)		
- **Pica& loss of appetite**	6 (20.7%)	6 (20.7%)		
CNS:	8 (27.6%)	13 (44.8%)	**	0.17
- **Loss of concentration**	21 (72.4%)	16 (55.2%)	1.87	
- **No CNS complaint**				
CVS:			***= 4.86	0.03
- **Shortness of breath, palpitation & easy fatigability**	19(65.5%)	26(89.7%)		
- **No CVS complaint**	10 (34.5%)	3 (10.3%)		
Abdomen:				
No abdominal complaint	29 (100%)	29 (100%)		
RBC (4.0-5.2x10^{12}/l)			****	0.228
- **Range**	3.2-3.5	3.6-3.9	1.207	
- **Mean ± SD**	3.5±0.3	3.6±0.4		
Hb(11-14.5gm/dl)			****	0.197
- **Range**	9.2-10.5	10-10.8	1.036	
- **Mean ± SD**	9.97±0.31	10.44±.026		
MCV (73.9-87.4fl)			****	0.207
- **Range**	61.4-72	56.9-74.3	1.263	
- **Mean ± SD**	66.2±3.6	67.5±5.2		
MCH (23.6-31.0pg)			****	0.125
- **Range**	18-24	18.9-24.6	1.042	
- **Mean ± SD**	20.44±1.6	21.7±2.02		
HCT (34-40)			****	0.202
- **Range**	28.2-33	27-35.6	1.65	
- **Mean ± SD**	30.49±1.2	31.9±2.4		
RDW	14.8-17.9	14-17.5	*****	0.054
- **Range**	16.19±0.799	15.71±1.028	1.969	
- **Mean±SD**				
PLT (150-450x10^3/mm^3)			****	0.107
- **Range**	354-543	208-528	2.718	
- **Mean ± SD**	465.55±76.9	393.1±112.6		

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WBCs (4-11 x10^3/mm^3)				
- **Range**	6.8-9.6	5.45-10.78	****	0.498
- **Mean ± SD**	8.58±0.9	8.5±1.8	0.677	
Serum Iron (50-120 µg/dl)			****	0.797
- **Range**	19-45	15-48	0.257	
- **Mean ± SD**	33±10	35±18		
serum. ferritin (12-300 ng/ml)			****	0.538
- **Range**	5-11	4-12	0.615	
- **Mean ± SD**	6±2.5	7±3.7		
TIBC (250-450µg/dl)			****	0.246
- **Range**	400-420	410-430	1.16	
- **Mean ± SD**	410±10	420±20		
TSAT (20-50%)			****	0.526
- **Range**	4.8-10	2-9	0.634	
- **Mean ± SD**	8.37±2.4	8.4±4.99		

*** Wilcoxon signed-rank test **= X^2 ***Fisher exact test **** U test *****t** student t test Significant non-significant (P-value ≥ 0.05), significant (P-value < 0.05), **RBCs** = red blood cells, **Hb** = Hemoglobin, **MCV** = Mean corpuscular volume, **MCH** = Mean corpuscular hemoglobin, **HCT** = Hematocrit, **RDW** = Red Cell Distribution Width, **PLT** = Platelets, **WBCs** = White blood cells, **S.Iron** = serum iron test, **TIBC** = Total iron-binding capacity.

Table III: Comparison of the laboratory investigation results between group (1) and group (2) after two months of treatment.

	Post - treatment		Test of significance	P-value
	Group (1) (n=29)	Group (2) (n=29)		
Weight	13.25-35	9.5-48.2	* =	0.227
- Range	20±6.4	21.3±12.5	1.207	
- Mean ± SD				
Height	90-134	80-138	* =	0.691
- Range	108.3±12.9	106.6±20.03	0.397	
- Mean ± SD				
BMI	14.2-21	12.9-25.3	* =	0.371
- Range	16.8±1.9	16.9±3.4	0.895	
- Mean ± SD				
General:	13(44.8%)	10(34.5%)	**	0.19
- Good general condition	2 (6.9%)	8(27.6%)	6.06	
- Pallor	2 (6.9%)	3 (10.3%)		
- Pica& loss of appetite	10 (34.5%)	5 (17.2%)		
- Pallor improved	2 (6.9%)	3(10.3%)		
- Increase appetite& pica disappear				
CNS:	2 (6.9%)	4(13.8%)	**	0.38
- Loss of concentration	6(20.7%)	9(31%)	1.94	
- Improvement of school performance	21(72.4%)	16(55.2%)		
- No CNS complain				
CVS:	9 (31%)	12(41.4%)	**	0.09
- Shortness of breath, palpitation & easy fatigability	10 (34.5%)	14(48.3%)	4.86	
- Shortness of breath improved	10(34.5%)	3(10.3%)		
- No CVS complain				
Abdomen:	29 (100%)	29 (100%)		
- No abdominal complaint				
RBC (4.0-5.2x10^{12}/l)	4.5-5.54	4.23-5.8	***	
- Range	5.1±0.3	5.2±0.49	0.945	0.345
- Mean ± SD				
Hb(11-14.5gm/dl)	10.4-11.3	10.5-11.8	****	0.335
- Range	10.8±0.3	11.2±0.2	0.984	
- Mean ± SD				
MCV (73.9-87.4fl)	65-75	63.2-75	****	0.017
- Range	69.9±2.9	71.6±3.9	2.382	
- Mean ± SD				
MCH (23.6-31.0pg)	21-27	19.2-28	****	0.046

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- Range - Mean ± SD	23.6±1.5	24.2±2.4	1.998	
HCT (34-40) - Range - Mean ± SD	32-36 33.5±1.1	31-37 34.4±1.7	**** 2.763	0.006
RDW - Range - Mean ± SD	14-16.8 15.61±0.69	13.9-16.5 15.49±0.84	***** 0.614	0.542
PLT (150-450x10^3 /mm^3) - Range - Mean ± SD	189-432 320.8±61.1	195-409 290.5±73.7	**** 1.565	0.118
WBCs (4-11 x10^3 /mm^3) - Range - Mean ± SD	5.45-11.7 7.8±1.7	6.9-10.78 8.5±1.1	**** 2.25	0.024
Serum Iron (50-120 µg/dl) - Range - Mean ± SD	52-90 77±12	47-100 75±20	**** 0.023	0.981
Serum ferritin (12-300 ng/ml) - Range - Mean ± SD	13-80 32.8±19.5	14.3-70.5 50.2±37	**** 1.269	0.205
TIBC (250-450µg/dl) - Range - Mean ± SD	320-380 350±25	320-400 310±70	**** 3.429	> 0.001
Transferrin saturation (20-50%) - Range - Mean ± SD	2.5-19 12.3±4.4	11-22 14.6±3.2	**** 2.398	0.016

*Wilcoxon signed-rank test **= X^2 *** Mann-whitney test (U) **** U test *****#t non-significant (P-value ≥ 0.05), significant (P-value < 0.05), highly significant (P-value ≤ 0.001), RBCs = red blood cells, Hb = Hemoglobin, MCV = Mean corpuscular volume, MCH = Mean corpuscular hemoglobin, HCT = Hematocrit, RDW = Red Cell Distribution Width, PLT = Platelets, WBCs = White blood cells, TIBC = Total iron-binding capacity.

Table IV: Comparison of side effects between group (1) and group (2).

	Side effects		Test of significance Z-test	P-value
	Group (1) (n=29) N (%)	Group (2) (n=29) N (%)		
- **Side effects detected**	6 (20.6)	24 (82.7)	* 4.47	> 0.001
- **Black stool**	6 (20.7)	9 (31)	* 0.6	0.55
- **Constipation**	0	6 (20.7)	* 2.16	0.03
- **Vomiting**	0	3 (10.3)	* 1.19	0.24
- **Gastric upset& abdominal cramps**	0	6 (20.7)	* 2.16	0.03

* Z-test non-significant (P-value ≥ 0.05), significant (P-value < 0.05), highly significant (P-value ≤ 0.001).

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Table V: Comparison of the clinical examination and laboratory investigation results of Group (1) before and after two-month treatment by micro-dispersed iron.

	Group (1) (n=29)		Test of significance	P-value
	Pre-treatment	Post- treatment		
Weight (kg)		13.25-35	*	> 0.001
- **Range**	12-35	20±6.4	4.55	
- **Mean ± SD**	19.2±6.5			
Height (cm)		90-134	*	0.023
- **Range**	90-134	108.3±12.9	2.271	
- **Mean ± SD**	108.1±3.03			
BMI	12.98-20.3	14.2-21	*	> 0.001
- **Range**	16.07±2.05	16.8±1.9	4.548	
- **Mean ± SD**				
General:			**	> 0.001
- **Good general condition**	13 (44.8%)	13 (44.8%)	19.33	
- **Pallor**	10 (34.5%)	2 (6.9%)		
- **Pica& loss of appetite**	6 (20.7%)	2 (6.9%)		
- **Pallor improved**	--	10 (34.5%)		
- **Increase appetite& pica disappear**	--	2 (6.9%)		
CNS	8 (27.6%)	2 (6.9%)	**	0.008
- **Lack of concentration**	--	6(20.7%)	9.6	
- **Improve school performance**	21 (72.4%)	21 (72.4%)		
- **No CNS complaint**				
CVS:			**	> 0.001
- **Shortness of breath, palpitation & easy fatigability**	19(65.5%)	9 (31%)	50	
- **Dyspnea improved**	--	10 (34.5%)		
- **No CVS complaint**	10 (34.5%)	10 (34.5%)		
Abdomen:				
No abdominal complaint	29 (100%)	29 (100%)		
RBC (4.0-5.2x10^{12}/l)		4.5-5.54	***	> 0.001
- **Range**	3.2-3.5	5.1±0.3	4.71	
- **Mean±SD**	3.5±0.3			
Hb(11-14.5gm/dl)		10.4-11.3	***	> 0.001
- **Range**	9.2-10.5	10.8±0.3	4.722	
- **Mean±SD**	9.97±0.31			
MCV(73.9-87.4fl)		65-75	***	> 0.001
- **Range**	61.4-72	69.9±2.9	4.756	
- **Mean±SD**	66.2±3.6			
MCH(23.6-31.0pg)		21-27	***	> 0.001
- **Range**	18-24	23.6±1.5	4.709	
- **Mean±SD**	20.44±1.6			
HCT(34-40)		32-36	***	> 0.001
- **Range**	28.2-33	33.5±1.1	4.729	
- **Mean±SD**	30.49±1.2			
RDW	14.8-17.9	14-16.8	****	> 0.001
- **Range**	16.19±0.799	15.61±0.69	= 6.275	
- **Mean±SD**				
PLT (150-450x10^3/mm^3)		189-432	***	> 0.001
- **Range**	354-543	320.8±61.1	4.706	
- **Mean±SD**	465.55±76.9			
WBCs (4-11 x10^3/mm^3)		5.45-11.7	***	0.007
- **Range**	6.8-9.6	7.8±1.7	2.716	
- **Mean±SD**	8.58±0.9			
Serum Iron (50-120 µg/dl)		52-90	***	> 0.001
- **Range**	19-45	77±12	4.71	
- **Mean±SD**	33±10			

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Serum ferritin (12-300 ng/ml)		13-80	***	> 0.001
- **Range**	5-11	32.8±19.5	4.711	
- **Mean±SD**	6±2.5			
TIBC(250-450µg/dl)		320-380	***	0.285
- **Range**	400-420	350±25	1.069	
- **Mean±SD**	410±10			
Transferrin saturation (20-50%)		11-22	***	> 0.001
- **Range**	4.8-10	14.6±3.2	4.713	
- **Mean±SD**	8.37±2.4			

*** Wilcoxon signed-rank test **= X^2 Pearson chi-square test *** U test,** #t: student t test ******Paired t Test** Non significant (p-value > 0.05) (P-value > 0.05) significant (P-value < 0.05), highly significant (P-value ≤ 0.001), **Kg** = Kilogram, **Cm** = centimeters, **BMI** = Body Mass Index, SD=standard deviation, **RBCs** = red blood cells, **Hb** = Hemoglobin, **MCV** = Mean corpuscular volume, **MCH** = Mean corpuscular hemoglobin, **HCT** = Hematocrit, **RDW** = Red Cell Distribution Width, **PLT** = Platelets, **WBCs** = White blood cells, **TIBC** = Total iron-binding capacity

Table VI: Comparison of the clinical examination and laboratory results of group (2) before and after two-month treatment by oral traditional iron.

	Group (2) (n=29)		**X^2**	**P-value**
	Pre –treatment	**Post- treatment**		
Weight (kg)			*	> 0.001
- **Range**	9-48	9.5-48.2	4.715	
- **Mean±SD**	20.48±12.5	21.3±12.5		
Height (cm)	80-138	80-138	*	0.008
- **Range**	106.3±20.03	106.6±20.03	2.64	
- **Mean±SD**				
BMI	12.49-25.2	12.9-25.3	* 3.581	> 0.001
- **Range**	16.3±3.8	16.9±3.4		
- **Mean±SD**				
General:			**	0.04
- **Good general condition**	10 (34.5%)	10 (34.5%)	10.19	
- **Pallor**	13 (44.8%)	8(27.6%)		
- **Pica& loss of appetite**	6 (20.6%)	3 (10.3%)		
- **Pallor improved**	--	5 (17.2%)		
- **Increase appetite& pica disappear**	--	3(10.3%)		
CNS:	13 (44.8%)	4(13.8%)	**	> 0.001
- **Lack of concentration**	--	9(31%)	13.76	
- **Improvement of school performance**	16 (55.2%)	16 (55.2%)		
- **No CNS complaint**				
CVS:	26(89.6%)	12(41.4%)	**	> 0.001
- **Shortness of breath, tachycardia & easy fatigue**	--	14(48.3%)	19.16	
- **Shortness of breath improved**	3(10.3%)	3(10.3%)		
- **No CVS complaint**				
Abdomen:	29 (100%)	29 (100%)		
- **No abdominal complaint**				
RBC (4.0-5.2x10^{12}/l)		4.23-5.8	***	> 0.001
- **Range**	3.6-3.9	5.2±0.49	4.381	
- **Mean±SD**	3.6±0.4			
Hb(11-14.5gm/dl)		10.5-11.8	***	> 0.001
- **Range**	10-10.8	11.2±0.2	4.655	
- **Mean±SD**	10.44±.026			
MCV(73.9-87.4fl)		63.2-75	***	> 0.001
- **Range**	56.9-74.3	71.6±3.9	4.707	
- **Mean±SD**	67.5±5.2			
MCH(23.6-31.0pg)		19.2-28	***	> 0.001
- **Range**	18.9-24.6	24.2±2.4	4.483	
- **Mean±SD**	21.7±2.02			
HCT(34-40)		31-37	***	> 0.001
- **Range**	27-35.6	34.4±1.7	4.557	
- **Mean±SD**	31.9±2.4			

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RDW	14-17.5	13.9-16.5	****	0.021
- **Range**	15.71±1.028	15.49±0.84	= 2.45	
- **Mean±SD**				
PLT(150-450x10^3 /mm^3)		195-409	***	> 0.001
- **Range**	208-528	290.5±73.7	4.554	
- **Mean±SD**	393.1±112.6			
WBCs (4-11 x10^3 /mm^3)		6.9-10.78	***	0.754
- **Range**	5.45-10.78	8.5±1.1	0.314	
- **Mean±SD**	8.5±1.8			
Serum Iron (50-120 µg/dl)		47-100	***	> 0.001
- **Range**	15-48	75±20	4.706	
- **Mean±SD**	35±18			
Serum ferritin (12-300 ng/ml)		14.3-70.5	***	> 0.001
- **Range**	4-12	50.2±37	4.705	
- **Mean±SD**	7±3.7			
TIBC(250-450µg/dl)		320-400	***	> 0.001
- **Range**	410-430	310±70	4.265	
- **Mean±SD**	420±20			
Transferrin saturation (20-50%)		11-22	***	> 0.001
- **Range**	2-9	14.6±3.2	4.552	
- **Mean±SD**	8.4±4.99			

*** Wilcoxon signed-rank test **= X^2 Pearson chi-square test *** U test **** Paired t Test** non-significant (P-value ≥ 0.05), significant (P-value < 0.05), highly significant (P-value ≤ 0.001), **Kg** = Kilogram, **Cm** = centimeters, **BMI** = Body Mass Index, **SD**=Standard deviation, **RBCs** = red blood cells, **Hb** = Hemoglobin, **MCV** = Mean corpuscular volume, **MCH** = Mean corpuscular hemoglobin, **HCT** = Hematocrit, **RDW** = Red Cell Distribution Width, **PLT** = Platelets, **WBCs** = White blood cells, **TIBC** = Total iron-binding capacity.

Discussion

In the FPP group, male children were 41.4%, while female children were 58.6%. In the FS group, male children were 24.1% and female children were 75.9%. Both groups were sex and age comparable with no statistically significant difference between them (P-value > 0.05) (Table I).

The results were in agreement with Angeles-Agdeppa et al. (14) who reported that the mean age of the children was 7.32 years old, and the age and sex distributions were similar between both groups and there was no statistically significant difference. Also, among those with iron deficiency, 51.3% were females and 48.7% were males. There was no sex-specific difference between both groups.

The results showed that there was no statistically significant difference (P-value > 0.05) regarding weight, height, BMI, general condition, CVS, CNS, and abdominal complaint between both groups before treatment. Regarding laboratory findings, the results showed that there was no statistically significant difference (P-value > 0.05) regarding RBCs count, Hb, MCV, MCH, HCT, RDW, WBCs count, platelet count, serum iron, serum ferritin, TSAT, and TIBC between both groups before treatment (Table II).

Regarding CNS complaints, the results were in agreement with Arcanjo, (15) who studied 100 children (students at public school). Forty-two out of 100 students presented learning difficulty (cases), while 58 did not (controls). Each group (case and control) presented 16 anemic participants. The prevalence ratio (prevalence of learning difficulty in children with anemia divided by the prevalence of learning difficulty in children without anemia) was 1.31. Mean Hb and serum ferritin levels of schoolchildren with learning difficulty were statistically lower when compared to those without identifying an association between iron status and learning difficulties Regarding Hb, MCV, serum ferritin, and TSAT, theresults were in agreement with Akin et al. (16) who studied 50 patients consisting of 35 boys and 15 girls with the mean age of 16,59 ± 1,68 months. The Hb thresholds of the world health organization were used to identify anemia (Hb < 11 g/dL

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for patients 6–59 months old, Hb < 11.5 for patients >59-month-old). IDA was defined as Hb values less than the world health organization thresholds with the presence of two or more of the following parameters; MCV less than 70 fl, serum ferritin below 30 mcg/L, and TSAT less than 16% which accept our results.

Regarding RDW, the results were contrary to Aulakh et al. (17) who studied 151 children (6 months-12 years) with microcytic anemia (MCV<75 fl) and were classified into IDA and non-IDA on the basis of serum ferritin and TIBC. They concluded that RDW had a limited specificity for the diagnosis of IDA among children with microcytic hypochromic anemia.

After two-month treatment with FPP in group1 and FS in group 2, the results showed that there was no statistically significant difference (P-value > 0.05) between both groups regarding weight, height, BMI, general condition, CVS, CNS, and abdominal complaint. Regarding laboratory findings, theresults showed that MCV, MCH, HCT, TSAT, and TIBC were significantly lower in the FPP than the FS group. Also, the results showed that there was no significant difference regarding Hb, RDW, RBCs count, platelet count, serum iron, and serum ferritin between the FPP and the FS group after treatment (Table III).

Regarding Hb, the current study was in agreement with Bopche et al. (18) who studied 154 children with IDA (Hb<10 g/dl). Children were randomized to receive therapy with either the oral micro dispersed iron (Group A; n=59) or the oral FS (Group B; n=59). All were given elemental iron 6 mg/kg/day, 30 minutes before meals. They found that the majority of cases in both groups showed a significant rise in Hb level after treatment.

Regarding Hb, the results were in agreement with Yasa et al. (7) who studied children older than six months of age diagnosed with IDA. Patients with Hb values below normal were tested for TSAT, serum iron, and serum ferritin levels. They were randomly divided into two groups, group 1 received FS and group 2 received micronized dispersed (once daily) at a total dose of 5 mg iron/ kg/ day. Significant improvement in Hb was observed in the first month of treatment in the micronized dispersed group and the FS group with an increase of more than 2 g/dL in both treatment groups by the fourth month. Also, they found that changes in Hb and HCT levels from baseline were not significantly different between treatment groups. Regarding TSAT , it improved from approximately 5% in each group at baseline to >20% with no significant difference between the groups, but against the current results, they reported that the increase in serum ferritin was almost two-fold lower in the micronized dispersed group versus FS.

The result showed that side effects were significantly lower in the FPP than the FS group. Constipation, gastric upset, and abdominal cramps were significantly lower in the FPP than the FS group after treatment, while there was no significant difference between both groups regarding vomiting and black stool (Table IV).

The result was in agreement with Christofides et al. (19) who studied 118 children diagnosed as IDA divided into five groups and received different types of iron therapy. They found that there was a significant increase in mean Hb concentration in each group but with no significant differences between groups.

The result was contrary to Khalid et al. (20) who studied 60 children, FS and micro dispersed iron were given in the dose of 5mg/kg/day. They reported that the mean rise in Hb concentration was significant and almost the same in children treated with either micro dispersed iron or FS for iron deficiency anemia after one-month and both FS and micro dispersed iron have comparable efficacy, but mean Hb rise with micro-dispersed iron was higher than with FS.

The results showed that weight, BMI, general condition, CVS, and CNS complaint were significantly improved in

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group 1 after two-month treatment with micronized dispersed iron (P-value < 0.05). Also, the results showed that RBCs count, Hb, MCV, MCH, HCT, serum iron, serum ferritin, and TSAT were significantly higher (P-value < 0.05), WBCs count, platelet count, and RDW were significantly lower (P-value < 0.05) in group 1 after two-month treatment with micro dispersed iron, while there was no significant difference regarding TIBC after treatment (P-value > 0.05) (Table V).

Regarding weight, height, Hb, MCV, MCH, RDW, and serum ferritin, the results were in agreement with Name et al. (21) who studied the effects of the FPP treatment on children with IDA and they found that there was a significant increase regarding weight, height, Hb and MCV, but there was no significant difference regarding MCH and serum ferritin level relative to the initial values.

Regarding weight, the results were in disagreement with yahav et al. (22) who studied the effects of the FPP treatment on children with IDA and they found that there was no significant increase regarding weight after treatment.

Regarding Hb, MCV, and MCH, the result was in agreement with Name et al. (21) who studied the effect of micro dispersed iron on children with IDA, they found that there was a significant increase in Hb, MCV, and MCH levels after treatment.

These results and that improvement regarding micro dispersed iron may be due to more tolerability, compliance, and fewer side effects of micro dispersed iron.

Regarding Hb, serum iron, MCV, and RDW the results were in disagreement with Yahav et al. *(22)* who studied the effect of micro dispersed iron on children with IDA, they found that there was no significant difference in Hb, serum iron, MCV, and RDW after treatment (Table V).

The study showed that weight, height, BMI, general, CVS, and CNS complain were significantly improved in group 2 after two-month treatment with oral traditional iron (FS). The study showed that RBCs count, Hb, MCV, MCH, HCT, serum iron, serum ferritin, and TSAT, TIBC and were significantly higher, RDW and platelet count were significantly lower while there was no significant difference regarding WBCs count in group 2 after two-month treatment with oral traditional iron (Table VI).

Regarding height and weight, the results were in agreement with Bobonis et al. (23) who studied the effect of FS treatment on children with IDA, they found that there was a significant increase in height and weight relative to the initial values after treatment.

Regarding height and weight, the current results were contrary to Wieringa et al. (24) who studied the effect of FS treatment on children with IDA. After treatment, they found that there was no significant difference in height and weight relative to the initial values.

The current study showed that RBCs count, Hb, MCV, MCH, HCT, serum iron, serum ferritin, TSAT, and TIBC were significantly higher., RDW and platelet count were significantly lower, while there was no significant difference regarding WBCs count in group 2 after two-month treatment with traditional oral iron *(Table 7)*.

Regarding Hb and serum ferritin values, the results were in agreement with Zlotkin et al. (25) who studied the effect of FS treatment on children with IDA, they found that there was significant increase in Hb and serum ferritin levels relative to the initial values.

Similarly, regarding Hb and serum ferritin values, the results were in agreement with Surkan et al. (26) who studied the effect of FS treatment on children with IDA, they found that there was a significant increase in serum ferritin levels, but it had little impact on Hb concentrations. The effect of iron treatment on Hb concentration was greater (but still not statistically significant) in children who were more anemic at the start.

Regarding serum ferritin, the results were in agreement with Singhal et al. (27) who

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studied the effect of FS treatment on children with IDA, they found that there was a significant increase in serum ferritin levels. They concluded that a marked rise in the serum ferritin may occur as early as a day or two after the initiation of iron treatment.

This result may be due to the salts of FS that have uniformly good bioavailability especially when taken on an empty stomach or between meals (28 and 29).

Conclusion

Micro dispersed iron could be used as an alternative therapy for children with IDA who refuse oral iron therapy in a liquid form with more tolerability and less side effects.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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