Impact Of 6 To 8 Weeks Iron Therapy On Psychomotor And Cognitive Development In Children Less Than 30 Months Old With Mild To Moderated Iron Deficiency Anemia (IDA); Observational Analytical Study

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Abstract

Background:
Iron deficiency anemia (IDA) is very common in young Indian children. Studies have suggested that IDA may affect a child's motor and cognitive function adversely with long-term consequences. We want to evaluate the benefit of iron therapy on psychomotor development and cognitive function in children 6-30 months of age with IDA.

Objective: To determine whether IDA affects cognitive and motor development in children and its reversibility after 6-8 weeks of iron therapy and whether the age of occurrence affects the outcome.

Methods and Material: In this prospective cohort study of 40 children [20 each in group A (6-18 months) and group B (19-30 months)] attending the well-baby clinic with mild to moderate microcytic hypochromic anemia (haemoglobin 7-11mg/dl) and ferritin <12ng/ml were recruited by convenience sampling. Motor developmental quotient (DMoQ) and Mental developmental quotient (DMeQ) were assessed by DASII (Developmental Assessment Scale for Indian Infants) at baseline. After 6-8 weeks of iron therapy haemoglobin, ferritin, and the DASII were re-assessed in each group and compared.

Results: Baseline mean haemoglobin in group A was comparable[9.295 (±0.098)] with Group B [8.688 (±0.881)] (p=0.065) which increased to 10.184 (±0.104) and 9.706 (±0.843) post-treatment respectively. (p<0.001). Both pretreatment DMoQand DMeQ in group A were significantly lower(81.7505±5.47536 and 80.2316(±10.18296) than in group B (88.3338±4.02698 and 88.6081±3.52993) respectively. (p<0.001). Post-treatment the DMoQ and DMeQ of group A increased to 89.5142 (±6.33824) and 87.1279(±9.41449) respectively. (p <0.001). The DMoQ and DMeQ of group B increased to 91.1719(±3.35625) and 91.3969(±2.57973) post-treatment respectively. (p <0.001). Posttreatment Hemoglobin, S.ferritin, DMoQ and DMeQ achieved in both groups were similar (p= 0.137, p=0.203, p=0.311 and p= 0.101 respectively).

Conclusions: Mild to moderate iron-deficiency anemia impairs Psychomotor and Mental development in Children <30 months. IDA affects DMoQ and DMeQ in children younger than 18 months of age more severely than in older children. The DMoQ and DMeQ improved after 6 to 8 weeks of iron therapy in both the groups but they remained below normal. Initial DMoQ and DMeQ score differences between study groups were not found to be significant after 6-8 weeks of oral iron treatment. Prevention, early recognition of IDA, and treatment with normalization of hemoglobin along with developmental support may be more beneficial.

Introduction:

The WHO Global Database on Anemia for 1993–2005, projected the prevalence of anemia worldwide at 25 percent [1]. Its prevalence is 9% in developed countries and almost 43% in low-development countries. Anemia affects 1.62 billion people globally with almost 293 million children of preschool age being affected and the most common nutrient deficiency in the world [2]. In India, as per the NFHS-5 data, 67.1 percent of children under five years of age are anemic and the predominant of them have an iron deficiency anemia[13]. Behavioral and cognitive dysfunctions are the most troublesome manifestations of iron deficiency. Iron is important for the normal development and functioning of dopaminergic neurons and its early changes could lead to permanent damage [3]. The important effects on neurotransmitter receptors during the early stages of iron deficiency suggest the deficits in both excitatory and inhibitory pathways of the central nervous system [4]. The likely biological basis of the behavioral and cognitive developmental delays seen in iron-deficient infants include a) abnormal neurotransmitter metabolism b) decreased myelin formation, and c) alterations in brain energy metabolism [4].

Infants with IDA have been found to have lower cognitive and motor test scores than infants without IDA in most [32,41] and long-term studies indicate that lower developmental test scores in infants with IDA persist years after the period of deficiency[29,38] and may not be reversible even with treatment. There is increasing evidence that marked iron deficiency can cause significant CNS damage even in the absence of anemia. [47,48]

Due to the Critical stage of development of the nervous system, impaired cognitive and motor development may be irreversible or only partially reversible after treatment of IDA depending on the time of onset, duration, and severity of IDA . [25]

A study in children aged 6 to 24 months investigating the effects of age and whether the developmental deficits observed was influenced by the timing of iron deficiency found lower but similar motor deficits across the age groups, while the cognitive deficits were lower and gradually worsened with increasing age with the older children with IDA affected the most.[42]

Follow-up studies after a course of iron therapy in IDA children have yielded mixed results.

Cochrane systemic review[5] which included 6 studies (225 children) that looked at the short-term effects of iron treatment within 30 days of starting treatment and found no improvement in scores on either the Bayley Scale Psychomotor Development Index (PDI) or the Bayley Scale Mental Development Index (MDI).[7,8]. Two other studies (160 children) looked at the long-term effects of iron treatment more than 30 days after starting it. One study found no effect of iron treatment on the acquisition of skills as measured by the Denver Developmental Screening Test [9]. The other study with 4 months of iron therapy found that scores on the Bayley scale, PDI, and MDI were significantly higher post-treatment for the group receiving iron treatment.[6]

With conflicting results, the absence of sufficient data on a longer duration therapy, the effect of age on the outcomes of iron therapy and the magnitude of IDA in India the present study is aimed to determine whether IDA affects cognitive and motor development in children and its reversibility after 6-8 weeks of iron therapy and whether the age of occurrence affects outcome [5].

METHOD

This prospective cohort study was carried out in a tertiary care hospital between September 2017 and July 2019. Institutional Ethics Committee clearance was taken (BVDU/Exam/5578/2017-18). Convenience sampling was used for enrolling children attending the well-baby clinic in the age group of 6 to 30 months of age and having mild to moderate iron-deficiency anemia (haemoglobin 7-11mg/dl, MCV< 70 fl and ferritin <12ng/ml) after parental consent. Children with severe anemia/ prematurity/ chronic diseases/having received previous iron treatment or prophylaxis were excluded from the study. A total of 40 children with 20 each in 2 age groups [group A (6-18 months) and group B (19-30 months)]. 35 (87.5%) cases were followed up (19 in Group A and 16 from Group B) and analyzed as 5 cases (12.5%) were lost to follow-up during the study period.[Figure.1]. Hemoglobin levels, MCV, MCH, MCHC (automated hematology analyzer (Sysmex Kx -21), and Ferritin values were documented (Acubind ELISA method).

Baseline Neurodevelopmental assessment was done by Developmental Assessment Scale for Indian Infants (DASII). DASII is an Indian modification of the Bayley scale of infant development containing motor and mental scales with 67 and 163 items, respectively. After the assessment of children, the motor development quotient (DMoQ) and mental development quotient (DMeQ) was calculated as per the manual of the DASII scale.[46] The motor scale assesses the control of gross and fine motor muscle groups. The mental scale assesses cognitive, personal, and social skills development. The age placement of the item at the total score rank of the scale is noted as the child's developmental age. This converts the child's total scores to his motor age (MoA) and mental age(MeA). The respective ages are used to calculate his / her motor and mental development quotients respectively by comparing them with his chronological age (CA) and multiplying it by 100. (DMoQ = MoA /CA x 100 and DMeQ = MeA /CA x 100). The DASII mean score is taken as a DQ of 100 and a standard deviation (SD) of 15.

A good correlation between developmental quotients (DQ) by DASII and social quotients (SQ) by Malin's Vineland Social Maturity Scale [VSMS]) has been shown.

Children of both groups were started with an oral iron preparation of 4mg/kg/day as per standard practice by the treating physician and were asked to follow up after 6-8 weeks post iron therapy. On follow-up, blood samples were collected for Hb, MCH, MCV, MCHC, and serum ferritin, and their psychomotor and cognitive developmental assessment was repeated with the DASII scale (Figure 1) by a trained psychologist who was unaware of both the baseline and post-treatment hemoglobin level.

Statistical analysis:

Data entry was done in an MS Excel spreadsheet and statistical analyses were done using computer software (SPSS version 20 and primer). The continuous measures were summarized as mean ± standard deviation. The mean change in HB, MCV, MCH, Ferritin, DMoQ, and DMeQ in both the groups pre and post-treatment were compared by a paired t-test. The baseline and post iron therapy DMoQ and DMeQ in the two age groups were compared with an unpaired t-test. Categorical variables were compared with a Chi-square test. The level of statistical significance was set at $P < 0.05$.

Results:

Baseline characteristics: (Table1)

Children were analyzed in groups A and B based on the age category. Their baseline Pre-treatment mean hemoglobin level was higher [9.299(±0.098)] in the younger age category(6-18 months) compared to 8.688 (± 0.881) in the older (19-30

months) children. (p<0.001). At the baseline, all the children from both groups had normal nutritional status; the mean hemoglobin level 9.299(±0.098) and 8.688 (± 0.881), the proportion of males (68.4% and 50%), mode of delivery, socioeconomic status, and the serum ferritin[6.098 (± 3.174) and 6.175(± 3.412)] levels were comparable in the two age group categories. The pretreatment DMoQ(81.7505±5.47536) and DMeQ 80.2316(±10.18296) in group A were significantly lower than in group B (88.3338±4.02698 and 88.6081±3.52993) respectively. (p <0.001)

Post-treatment follow up: (Table 2 and Table 3)

Post-treatment in group A(6-18 months) the mean hemoglobin levels increased from 9.295(±0. 0.9964) to 10.18(±0.968) (p <0.001), mean ferritin levels increased from 6.098 (± 3.174) to 33.768 ± 9.104) (p value <0.001).
The mean DMoQ increased from 81.7505(±5.47536) to 89.5142 (±6.33824) (p value <0.001) and mean DMeQ increased from 80.23(±10.18296) to 87.1279(±9.41449) (p value <0.001).

Post-treatment in group B (19-30 months) the mean haemoglobin levels increased from 8.68(±0.8816) to 9.70 (±0.8835). (p-value <0.001), mean ferritin levels increased from 6.175 to 37.719 (p-value <0.001).
The mean DMoQ increased from88.3338± 4.02698 to 91.1719(±3.35625) and (p-value <0.001) and mean DMeQ increased from 88.6081±(3.52993) to 91.3969(±2.57973) (p-value <0.001).
Posttreatment Hemoglobin, S.ferritin, DMoQ and DMeQ achieved in both groups were comparable(p= 0.137, p=0.203, P = 0.311 and P = 0.101 respectively). (Table 4 and Table 5).

Discussion:

Iron-deficiency anemia (IDA) in infancy and early childhood has been consistently shown to negatively influence performance in tests of psychomotor and cognitive development, in more than a dozen studies during the last two decades. We had enrolled children with mild to moderate IDA who otherwise had normal physical growth.
It was observed that the pre-treatment motor DQ and mental DQ scores were lower in children 6-30 months of age with IDA compared to the standard normative cut-off scores of Indian children [mean(SD) of 100±15] by 18.25 points and 19.77 points in the younger and by 11.60 points and 11.67 points older group respectively. Though most had a mild delay, this clearly shows the adverse impact of IDA on motor and mental development even with mild to moderate IDA.
Both the psychomotor and cognitive development in the younger children(6-18 months) was more affected than the older children (19-30 months). The earlier age is the critical period of brain development. Having IDA earlier may have led to a more severe deficit in the younger children compared to the older children. However, Lozoff had observed that though the psychomotor development is lower and comparable across the age groups of 6-24 months in children with IDA, the cognitive development suffered the most in the older children compared to younger children with IDA. He concluded that both the age of onset and severity contributed to the more observed deficits in older children. He also noted that the effects or the deficits may be detectable in older infants because of the increased sensitivity of infant development tests in the second year of life. [42]. Our cohort of older children was however less affected compared to the younger group. It could be either because of later-onset of IDA beyond the earlier most vulnerable period of development and also lesser duration of exposure to IDA in the older group as the exact age of onset of anemia was unknown.
In our study giving iron therapy for 6-8 weeks resulted in significant improvement in haemoglobin, and ferritin status but haemoglobin levels in all children remained in the mild anemia range. This is probably due to the shorter duration of treatment of IDA. The optimal duration is said to be 3 months after anemia has been corrected, to replenish the iron stores. This was associated with an improvement of DMoQ and DMeQ in both groups. Though both our cohorts had a significant improvement in DMoQ and DMeQ compared to the baseline, they failed to catch up with the standard norms for Indian children.
Studies looking at post-treatment DMoQ and DMeQ scores on the Bayley scale in IDA children who offered short-term treatment i.e. less than thirty days with most of them offering treatment less than eleven days found that there was no improvement [7, 8]. The smaller sample size and the possibility of a longer duration may be required to develop the skills that are measured by these developmental tests(Bayleys scale) may have contributed to the failure of these studies to demonstrate an effect. Longer duration iron treatment of IDA in children i.e. more than thirty days has revealed conflicting results. A study by Aukett et al [9] with a cohort of 97 children found no benefit of giving iron therapy for two months on the acquisition of skills as measured by the Denver Developmental Screening Test. Other studies with a longer duration of iron therapy i.e four months [6] and three months of iron [43,49] which resulted in the correction of IDA anemia and iron deficiency in most infants had significantly better developmental scores as measured on the Bayleys scale, with no significant post-treatment difference between the mean mental development scores of the iron-treated IDA infants and of the iron or placebo-treated iron-sufficient infants. Their results suggest the almost complete reversibility of deficits after a longer duration of iron treatment. However, Lozoff in their study on the effect of long-term therapy for 6 months found that developmental deficits of anemic subjects persisted despite correction of IDA.[38]. The differences in the social background may account for these disparities in the response.

The partial improvement in DMoQ and DMeQ without normalization in our study could be because of the incomplete improvement of haemoglobin levels with persisting mild anemia in most treated children due to the shorter duration of 6-8 weeks of iron therapy. Lozoff [38] found that children with moderate anemia and even the children with hemoglobin> 10 gm/dl who had not normalized their hemoglobin levels after treatment had poorer outcomes post-treatment which persisted even at five years of age. A longer duration of therapy with complete correction of anemia has been demonstrated to completely reverse developmental deficits. [6,43] . This suggests that though both the younger and older children have the potential to improve their motor and cognitive development post-treatment, failure to correct the anemia post-treatment may lead to persisting deficits in developmental scores both in the short and longer-term. A longer duration of treatment of IDA which completely reversed the developmental deficits as in other studies[6,43] may have completely corrected the anemia in our cohort too and probably achieved a higher DMoQ and DMeQ score in them.

We had also hypothesized that the younger age group was more vulnerable to the effects of IDA which may lead to irreversible damage to the motor and cognitive development with lower improvement in development scores as compared to older children in whom IDA may be transient and reversible. Lozoff et al [45] suggested that there are critical periods in which IDA might have long-term effects on cognition and behavior (eg, infants aged <1 year, and preschool children). In our study, both groups improved their DMoQ & DMeQ, albeit lower than normal. The younger group had lower motor and mental scores at baseline compared to the older subgroup, however, the improvement in the psychomotor development score in the iron-treated IDA younger subgroup was larger, and the difference in the developmental scores achieved among the groups post-treatment was not present. Grantham et al[18] concluded that the benefit of short-term iron treatment in anemic children aged,< 2 years is controversial and in anemic children aged >2 years, iron treatment would be more effective with most showing improvement in cognition. Other studies like Walter et al [8] who compared the effects of IDA in a much younger cohort of 127 children (aged 0 to 15 months) and an older cohort of 43 children (aged 5 years) concluded that infants with IDA at 12 months of age who showed poorer developmental test performance at the time of original assessment showed persistence of lower test despite subsequent iron therapy.
The other possible reason for the non-difference in the final i.e. post-treatment DMoQ/ DMeQ in our cohorts could be because although both groups had anemia, the timing of onset in them was not known. The older children may have had an earlier age of onset of IDA like the younger group, which was detected late and the prolonged duration of anemia led to some irreversibility. Hence they fared no better than younger children with IDA post-treatment in the final motor and mental DQ scores. Thus motor and mental test scores in both age cohorts with mild to moderate IDA were only partially reversible post-treatment. Prolonged treatment with iron may have helped achieve better test scores.

Limitations:
In our study sample, most of the families were in the lower-middle class, and all of the children were normal in their nutritional status. However, the other potential confounders like maternal warmth, maternal mental health and IQ, birth weight, duration of breastfeeding, and other environmental factors were not accounted for. Some of these factors have not been found to account for the difference in motor and mental developmental test scores.[43]. It is possible that some of the environmental or family factors, measured and unmeasured, could partly or completely explain these findings. We had not included a control arm of non-anemic children or a placebo arm in our cohort of IDA children as it may be unethical to do so in anemic children.
Having a larger sample size from the community, the presence of a control arm of non-anemic children, or randomization of treatment with a placebo in one arm may have helped us to avoid the known and unknown potential confounders. This would have helped generalize the results from our study to all children in the said age group. The other limitation was that though the severity of anemia was known in all children, the time of onset and thus its duration in either group was unknown. Hence it was not possible to conclude regarding the contribution of either the longer duration or age of onset of IDA on the development test scores post-treatment.

Conclusion-

Iron deficiency anemia in early infancy and childhood led to reduced psychomotor and cognitive development in children aged 6-30 months. Treatment with iron may lead to improvement of motor DQ and Mental DQ, iron supplementation alone seems to be insufficient and some adverse impacts on development scores may persist. This may be the point to the fact that the poor development is not caused by anemia or that the effect is irremediable by iron therapy alone. Improvements in the environment and additional development interventions may help these anemic children to catch up and optimize their developmental outcomes. The prospect of its irreversibility and persisting deficits is daunting. Considering the very high prevalence of IDA in Indian children the burden of underperformance could affect the future of our nation. Equally encouraging is the fact that iron therapy may improve the lagging psychomotor development. If we can prove this in a larger study then an early screening of IDA, universal prophylactic iron therapy in infancy, food supplementation with early identification and prompt treatment of IDA, and thorough developmental assessment and intervention are warranted in addition to iron therapy.

What is already known:
Iron deficiency anemia causes psychomotor and cognitive developmental delay. Older studies observed no significant improvement in developmental scores after short-term iron therapy with a longer duration iron therapy results were inconclusive. There was also a difference in improvement in motor and cognitive outcomes between younger vs older children with IDA.

What this study adds:
Mild to moderate IDA impacts psychomotor and cognitive development in children 6-30 months of age. They improve post six to eight weeks of iron therapy significantly. However, it is not completely reversible. There was no difference in the final improvement of developmental scores between younger vs older aged children with mild to moderate IDA.

Figure 1:

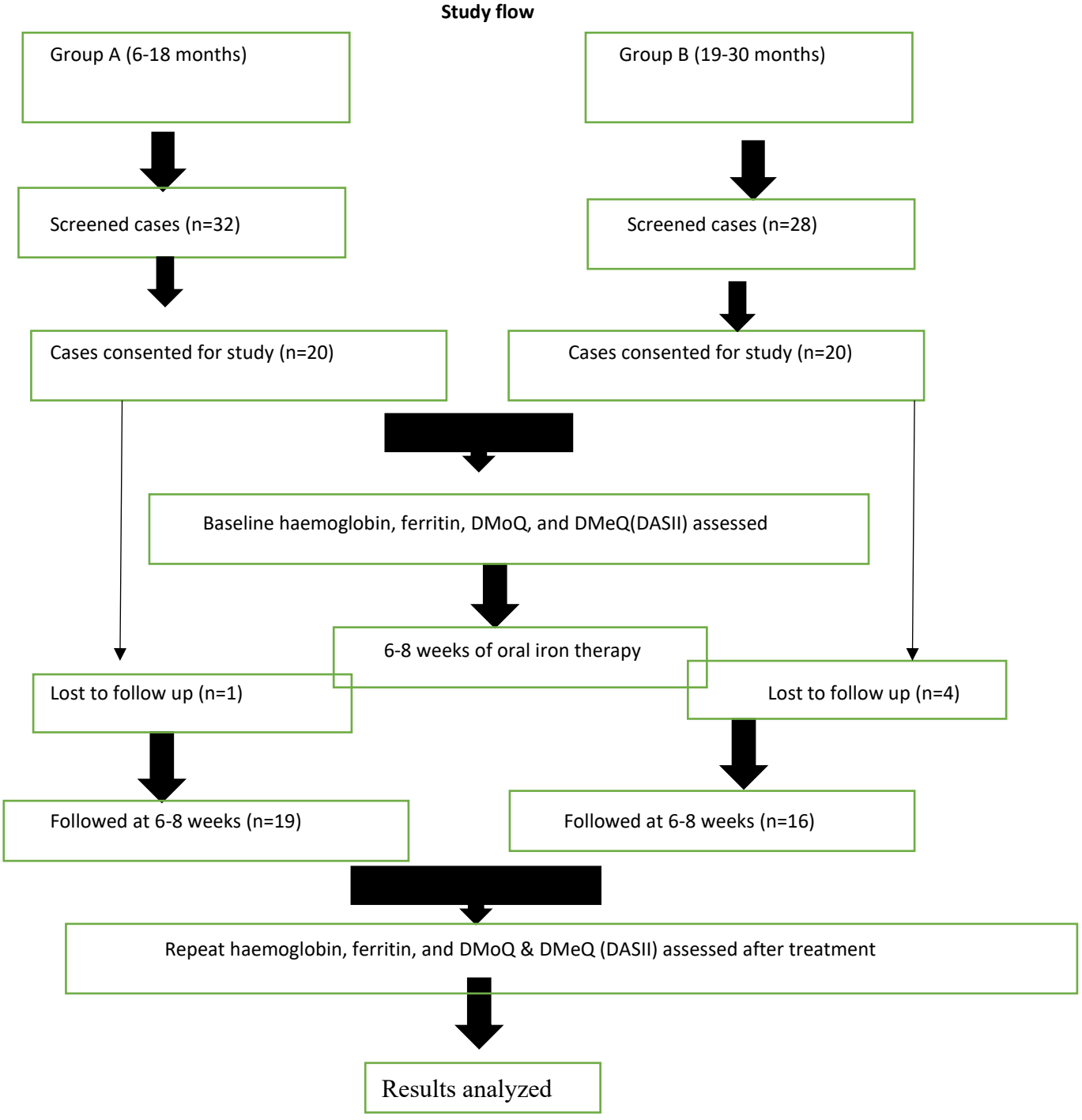

Table 1: Baseline characteristics in the two age categories

Characteristics		Group A(n=19) (6-18 months)	Group B(n=16) (19-30 months)	
Gender	Male	13 (68.4%)	8 (50%)	P= 0.268
	Female	6 (31.6)	8 (50%)	
Mode of Delivery	Vaginal	13 (68.4%)	6 (37.5%)	P = 0.067
	LSCS	6 (31.6)	10 (62.5%)	
Nutritional status	(z scores <-2)	0	0	
Socio Economic status	Lower middle class	19 (100%)	16 (100%)	
Mean Hb	Pre iron therapy	9.295 (± 0.098)	8.688 (± 0.881)	P = 0.065
Mean Ferritin	Pre iron therapy	6.098 (± 3.174)	6.175(± 3.412)	P = 0.9397
Mean DMoQ	Pre iron therapy	81.7505(±5.475)	88.3338(±4.027)	P< 0.001*
Mean DMeQ	Pre iron therapy	80.2316(±10.18296)	88.6081(± 3.52993)	P< 0.001*

Chi-square test for proportions and Unpaired t-test for comparison of means.
*significant p values

Table 2 Comparison of pre and post-treatment Hemoglobin(Hb) and Ferritin in both age groups					p-value
		Mean	Number	SD	
Group A (6-18 months)	Pre treatment Hb	9.295	19	0.9964	p<0.001*
	Post treatment Hb	10.184	19	0.9680	
Group B (19-30 months)	Pre treatment Hb	8.688	16	0.8816	p<0.001*
	Post treatment Hb	9.706	16	0.8835	
Group A (6-18 months)	Pre treatment Ferritin	6.098	19	3.1740	p<0.001*
	Post treatment Ferritin	33.768	19	9.1040	
Group B (19-30 months)	Pre treatment ferritin	6.175	16	3.4118	p<0.001*
	Post treatment Ferritin	37.719	16	8.8438	

Paired t-test for comparison of means. *significant p values

Table 3 Comparison of pre and post-treatment DMoQ and DMeQ in both age groups					p-value
		Mean	Number	SD	
Group A (6-18 months)	Pre treatment DMoQ	81.750	19	5.4753	p<0.001*
	Post treatment DMoQ	89.514	19	6.3382	
Group B (19-30 months)	Pre treatment DMoQ	88.333	16	4.0269	p<0.001*
	Post treatment DMoQ	91.171	16	3.3562	

Group A (6-18 months)	Pre treatment DMeQ	80.231	19	10.182	p<0.001*
	Post treatment DMeQ	87.127	19	9.4144	
Group B (19-30 months)	Pre treatment DMeQ	88.608	16	3.5299	p<0.001*
	Post treatment DMeQ	91.396	16	2.5797	

Paired t-test for comparison of means. *significant p values

Table 4 Comparison of post-treatment Hemoglobin(Hb) and Ferritin between the two age groups					p-value
		Mean	Number	SD	
Hemoglobin	6-18 months	10.184	19	0.9680	P=0.137
	19-30 months	9.706	16	0.8835	
Ferritin	6-18 months	33.768	19	9.1040	P=0.203
	19-30 months	37.719	16	8.8438	

Unpaired t-test for comparison of means

Table 5 Comparison of post-treatment DMoQ and DMeQ between the two age groups					p-value
		Number	Mean	SD	
DMeQ	Group A (6-18 months)	19	89.5142	6.3382	0.311
	Group B (19-30 months)	16	91.1719	3.3562	
DMeQ	Group A (6-18 months)	19	87.1279	9.4144	0.101
	Group B (9-30 months)	16	91.3969	2.5797	

Unpaired t-test for comparison of means.

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