Role of low dose iron intake on acute respiratory tract infection in infants: A longitudinal study

Divyanshu Agrawal[1], ***Shetanshu Srivastava**[2]

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Abstract

Background: Anaemia and respiratory tract infections are common problems among infants and a complex relationship exists between iron status and infection. Studies on possible role of iron supplementation to prevent respiratory tract infection in healthy infants are needed so that strategies could be made at the community level to reduce its burden.

Objectives: To study the effect of iron intake on the incidence of acute respiratory infection (ARI) in healthy infants.

Method: A longitudinal study was done in 106 infants at the paediatric department of a teaching hospital, in which infants coming for routine vaccination with haemoglobin levels ≥10g/dl were divided into two groups after computer generated randomization. Group A received 2mg/kg/day of iron for 3 months and Group B received no supplementation. Episodes of respiratory tract infection were recorded. Follow up was done at 4, 8 and 12 weeks and at 6 months for new episodes of ARI. Growth was monitored. Data were analysed using Mann-Whitney U test, Chi square test and Student 't' test via SPSS version 20.0.

Results: After 6 months of follow up, mean haemoglobin in the iron supplemented group (12.76±0.63g/dl) was significantly higher than in the non-supplemental group (11.29±0.98g/dl) ($p<0.001$), when the baseline haemoglobin levels in both groups were comparable. The incidence of ARI was 66% lower in the iron supplemented group compared with the group with no supplementation (IRR=0.34, 95%CI=0.19-0.59, p=0.0001)

Conclusions: Iron supplementation in infants improves their haemoglobin status and decreases episodes of ARI in them.

(Key words: Anaemia, Acute respiratory infections, Infant, Iron)

Introduction

Acute respiratory infection (ARI) is responsible for an estimated 3.9 million deaths worldwide, with 90% deaths due to bacterial pneumonia in young children[1]. ARI contributes to 15-30% of under-five deaths in children and most of these deaths are preventable[1]. On an average, children below 5 years of age suffer about 5-6 episodes of ARI per year[2]. According to the National Family Health Survey-4 (NFHS-4), many children with ARI cannot avail of treatment because they are not taken to a health facility[3]. So, some strategies are needed to reduce the risk factors for respiratory infections. Anaemia and respiratory tract infections co-exist. Incidence of iron deficiency among children aged 6 to 36 months is high, ranging from 74.6% to 81.7%, the age when repeated respiratory infections occur[4]. Children with iron deficiency anaemia are 4.6 times more susceptible to such infections[5]. However, iron supplementation in healthy infants may prevent anaemia and in turn reduce ARI in them which needs to be evaluated. Studies substantiating our hypothesis are few to the best of our knowledge[6]. Though some studies show a reduced prevalence of respiratory and gastrointestinal infections with oral iron therapy in anaemic children, others show an increase or no change in the incidence of infectious disease[7-10].

Objectives

To assess the effect of iron supplementation on ARI in healthy infants.

Method

A longitudinal study was done in the department of paediatrics of a teaching hospital. We included infants of 9 months [+2 weeks] age with a haemoglobin level ≥10g/dl attending the immunization clinic. Infants having a history of ARI

[1]*Assistant Professor, Department of Paediatrics, KD Medical College Hospital and Research Centre, Mathura, Uttar Pradesh, India,* [2]*Additional Professor, Department of Paediatrics, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India*
**Correspondence:* drsitanshu@yahoo.co.in
https://orcid.org/0000-0001-5054-0521
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or any acute infection in the last 2 weeks or who were on iron or vitamin supplementation and infants with severe acute malnutrition were excluded. A total of 106 infants were randomized into two groups by computer generated numbers; 53 infants in Group A received 150ml of iron solution. Remaining were non-supplemented group B. Infants in group A received iron (ferrous ascorbate containing 30mg of elemental iron/5 ml of solution) as a supplement in a dose of 2 mg/kg/day of elemental iron for a period of 3 months. Group B did not receive any intervention. Follow up was done at 4, 8 and 12 weeks of supplementation and then at 6 months.

Mothers were counseled to report all the episodes of respiratory tract infection with symptoms like fever, running nose, cough, sore throat, fast breathing, and any other symptom of illness like vomiting, ear ache or loose stools. Any infant with an episode of cough and fast breathing was advised physical consultation in the hospital at the earliest. Teleconsultation was also available. Haemoglobin level and anthropometric variables were recorded at the time of enrollment at 9 months of age, categorized as baseline and thereafter at follow up visit after 6 months and the mean frequency of symptoms reported by parents of infants were recorded at 4 weeks, 8 weeks, 12 weeks and 6 months of follow up.

Compliance with the intervention was monitored by asking the mother whether the iron syrup was given and by measuring the amount of solution remaining in the bottle when the patient came for the follow-up and when found empty, then the same bottle was provided. Infants who received the study drops <75% of the days during the study period were considered as 'non-compliant'. If repeated vomiting, intolerance, or any other acute illness, was found during the supplementation, supplement was withheld and if the symptoms of illness persisted on missing dose of supplement because of any reason was more than 3 weeks then they were excluded from the analysis. Episodes of respiratory illness were considered separate if there were ≥5 symptom-free days between the episodes[11]; 6 infants from group A (3 lost to follow up, 3 were non-compliant) and 8 from Group B were lost to follow up. Hence, 47 infants in group A and 45 infants in group B were analysed in the study.

Anaemia was defined as a haemoglobin level in blood less than 11g/dl with mild anaemia as haemoglobin level between 10–11 g/dl[12].

Acute respiratory infection *(ARI*) was an acute infection of any part of respiratory tract and related structures including paranasal sinuses, middle ear, and pleural cavity, including a diverse group of diseases ranging from self-limiting illnesses to bronchiolitis and pneumonia that may require medical care[13].

Ethical issues: Approval for the study was obtained from the Institutional Ethics Committee of Era's Lucknow Medical College and Hospital, Lucknow, India (No. ELMC/RCell/EC/2016/83). Written informed consent was taken from the parents of the participants.

Statistical analysis: The data were collected and checked for accuracy and the statistical analysis was done using Statistical Package for Social Sciences version 20.0 software. The values were represented in Number (%) and Mean ± SD. The Mann-Whitney U-test was used to compare mean number of episodes. The unpaired t-test was used to compare continuous variables. Chi-square test was used to compare categorical variables. The incident rate ratio with its 95% confidence interval (CI) was also calculated. p-value <0.05 was considered significant.

Results

Out of 92 infants completing the study, there was no statistical difference in mean age, male: female ratio and anthropometric parameters at the time of enrollment in both groups (Table 1).

Table 1: ***Demographic profile***

Characteristic	Group A (n=47) Iron supplemented group	Group B (n=45) Non supplemented group	Student 't' test
Age (months): Mean ± SD	9.19 ± 0.13	9.20 ± 0.12	't'=0.322; p=0.748
Gender: n (%) Male Female	 25 (53.2) 22 (46.8)	 32 (71.1) 13 (28.9)	$\chi 2$=3.132; p=0.077
Weight (kg): Mean ± SD	8.11± 0.71	8.16 ± 0.070	't'=0.380; p=0.705
Length (cm): Mean ± SD	71.57 ± 1.41	72.17+1.63	't'=1.863; p=0.066

Table 2 is a comparison of haemoglobin levels and anthropometric parameters. The mean haemoglobin levels of Group A were significantly higher than those of Group B on follow-up (p<0.001). There was no statistically significant differences on anthropometric parameters (weight and length) in groups A and B on follow up (p>0.05), which indicates that growth was not affected in the iron supplemented group.

Table 2: ***Comparison of haemoglobin levels and anthropometric parameters***

Parameter	Infant's age (Visit)	Group A (n=47) Iron supplemented group		Group B (n=45) Non supplemented group		Student 't' test	
		Mean	SD	Mean	SD	't'	'p'
Haemoglobin (g/dl)	Baseline	11.33	0.55	11.35	0.48	0.178	0.859
	6 months	12.76	0.63	11.29	0.98	-8.608	<0.001*
Weight (kg)	Baseline	8.11	0.71	8.16	0.70	0.380	0.705
	6 months	9.70	0.61	9.82	0.69	0.904	0.368
Length (cm)	Baseline	71.57	1.41	72.17	1.63	1.863	0.066
	6 months	78.29	1.31	78.72	1.65	1.400	0.165

**Significant*

Table 3 gives the incidence of ARI. Incidence of ARI was 66%, significantly lower in the iron supplemented group than in the non-supplemental group (IRR=0.34, 95%CI=0.19-0.59, p=0.0001).

Table 3: ***Incidence of acute respiratory infections (ARI)***

Outcome	Group A Iron supplemented group		Group B Non-supplemented group		IRR (95%CI), p-value
	Mean no. of episodes	Incidence#	Mean no. of episodes	Incidence#	
ARI	0.46	0.49±0.72	1.33	1.39±1.11	0.34 (0.19-0.59), 0.0001*

*#Per child-year observed, incidence rate = no. of episodes /total days observedX365, IRR=Incident rate ratio, *Significant*

The mean number of ARI episodes was lower in the iron supplemented group compared to the non-supplemented group at all time periods and it was statistically significant at the 6-month of follow-up (Table 4). The total mean number of episodes of vomiting was 0.09 in the iron supplemented group and 0.13 in the non-supplemental group.

Table 4: ***Week-wise mean number of episodes of acute respiratory infection (ARI) on follow-up***

Follow-up period	Group A Iron supplemented group	Group B Non-supplemented group	p-value[1]
12 weeks ARI	0.09 ± 0.28	0.16 ± 0.36	0.30
6 months ARI	0.23 ± 0.52	0.96 ± 0.87	0.0001*

*[1]Mann-Whitney U test, *Significant*

Discussion

The association between anaemia and respiratory tract infections has been described in a number of previous studies[5,6,15,16] which have recommended iron supplementation among anaemic children as a measure to check the incidence of ARI in them. However, there are few studies evaluating the impact of low dose iron supplementation on the ARI rate. A systematic review[17] has attempted to evaluate this but, owing to high heterogeneity, it failed to elucidate the role of iron supplementation on ARI. Hence, the present study was planned to evaluate the role of iron supplementation on ARI infection in infants.

The dose selection in the present study is in accordance with the WHO recommended daily iron supplementation for children aged 6-23 months, living in settings where anaemia is highly prevalent[18]; WHO recommends supplementation of 10-12.5 mg/day elemental iron to all children aged 6-23 months, though some studies have reported dosage as high as 200 mg/day[19]. In our study, infants had only mild anaemia (10-11g/dl) or no anaemia (>11g/dl); secondly, in view of previous studies[20] reporting a toxic impact of iron supplementation in infants and children, the dose was rationalized. Low-dose iron supplementation interventions in children <23 months of age have also been evaluated previously using 2-3mg/day elemental iron supplementation and found it to be safe[21-23].

At baseline, mean haemoglobin levels were matched in both study groups. However, after 6 months of follow up, mean haemoglobin levels were significantly higher in the intervention group. Mean haemoglobin levels were 12.5% higher as compared to baseline values, thus showing a significant increase in mean haemoglobin levels. These findings are in agreement with the observations of another study[21], which showed that the supplemented group had significantly higher mean haemoglobin levels as compared to the group without supplementation. Some other studies[23,25] also showed that children supplemented with iron had improved haemoglobin levels with lower risk of anaemia and iron deficiency. However, with respect to anthropometric parameters like weight and length, no statistically significant difference was observed between the two groups, thus showing that iron supplementation did not help in influencing their growth trajectory. Similarly, Pasricha SR, *et al*[24] in their systematic review did not find a significant impact of iron supplementation on weight gain and other anthropometric parameters.

On evaluating the role of supplementation on different morbidities at different follow up intervals, we found a significant difference for the number of ARI at 6-months of follow-up. For all these morbidities, the mean event rate was lower in iron supplemented group as compared to the non-supplemented group. These findings suggest that iron supplementation had an effect on these morbidities. There are mixed reports regarding the impact of iron supplementation on morbidity profile. Pasricha SR, *et al*[24] showed that there was no significant difference in events of ARI in both iron supplemented group and placebo group. One reason for this could be the fact that in the present study, we had included healthy infants who were mildly anaemic/non-anaemic but in other studies sample size, inclusion criteria and dose of supplementation were different[5,6,26,27]. They included severely malnourished and anaemic children[24] and hence the difference in outcome. Similarly, Berger J, *et al*[28] noted no evidence of an effect from iron supplementation on prevalence of respiratory infections. In the present study, we saw that in the iron supplemented group, there was a significant increase in haemoglobin and iron being part of various enzymatic processes in the healthy state, could be the reason for the lower susceptibility to different morbidities[29]. On overall evaluation, we found recurrence of ARI to be significantly lower in the supplemented group (44.7%) as compared to the non-supplemented group (82.2%). This is significant with a low dose supplementation of iron. This finding thus shows that the overall incidence of ARI and its recurrence was positively affected by iron supplementation in healthy infants.

In the present study, we did not find any significant difference between the two groups with respect to episodes of vomiting but in the systematic review of Pasricha SR, *et al*[24], they reported the incidence of vomiting to be significantly higher in the supplemented group. This could be due to the dose of iron supplementation.

One limitation is that we did not evaluate the iron store status of infants at any time in our study; hence we could not evaluate the effect of iron supplementation on iron reserves. We also did not evaluate the potential confounders like living conditions and feeding pattern which could have affected the iron status. However, we minimized the confounders by excluding malnourished severely anaemic infants and counselling about proper complementary feeds at every follow-up. Supplemental dose of iron in the study group resulted in no/few adverse effects like diarrhoea which were recorded only on follow-up. Moreover, a long term follow up is warranted to understand the impact of iron supplementation on respiratory tract infections. The findings of the present study are encouraging, highlighting the preventive aspects of ARI. It showed that iron supplementation was safe in infants, increased their haemoglobin levels and decreased episodes of respiratory tract infections in them.

Conclusions

Iron supplementation in infants improves their haemoglobin status and decreases episodes of ARI in them.

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