ORIGINAL ARTICLE

EFFICACY AND SAFETY OF INTRAVENOUS IRON IN CHILDREN WITH IRON DEFICIENCY ANAEMIA POORLY COMPLIANT TO ORAL IRON THERAPY

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Background: Iron deficiency is the most common nutritional deficiency worldwide. Common causes of IDA in children are excessive consumption of cow's milk and prolonged breast feeding with delayed and poor weaning. Oral iron is the first line of treatment in children with IDA but occasionally there is inadequate response due to poor compliance. The objective of this study is to assess the effectiveness and safety of intravenous iron in children with IDA, poorly compliant to oral iron therapy. **Methods:** This study consisted of 90 children from 12–60 months with IDA who were not responding adequately to oral iron therapy. Total iron requirement was calculated and given intravenously (IV) in two divided doses over two consecutive days. Participants were followed up at 2 and 4 weeks to assess the rise in haemoglobin level. Any adverse event was also noted. SPSS version 25 was used for statistical analysis. **Results:** Of the 90 enrolled children the mean age was 23.1±10.7 months, 47 (52.2%) were males and 43(47.8%) were females. The mean ferritin level before IV iron therapy was 3.75±2.53 ng/ml and mean haemoglobin was 5.9±1.3 g/dL. After IV iron therapy the haemoglobin level was raised to 8.38±1.09 g/dl and 9.74±0.88 g/dl at 2 and 4 weeks respectively which was statistically significant (p<0.05). The adverse events were fever in 3 (3.3%) and urticaria in 2 (2.2%) patients. **Conclusion:** Intravenous iron therapy is effective and safe to raise the haemoglobin levels in children with IDA who are poorly compliant to oral iron therapy.

Keywords: Children; Effectiveness; Iron deficiency anaemia; Intravenous iron therapy

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INTRODUCTION

Iron deficiency is the most common nutritional disorder worldwide.[1] The global burden of iron deficiency was around 43% and it was 7–9% in USA while it was as high as 70% in central & west Africa.[2] It is prevalent not only in developing countries but also in the developed world.[3,4] Iron deficiency encountered during antenatal period and in the first two years of life results in motor, social & cognitive impairment and poor growth.[5,6] To supply the essential iron for new RBCs and muscle cells, children should have 30% of the routine daily allowance of iron mainly from their dietary sources.[7] The sensitization of physicians for replenishing the iron stores have increased over the last few years.[8]

If iron deficiency is left unaddressed it will ultimately lead to iron deficiency anaemia (IDA). It is recommended to have universal screening of all children at one year of age by complete blood count.[9] World Health Organization recommends the use of oral iron supplementation by the age of six months in settings where IDA is prevalent.[10]

Iron deficiency mainly affects patients with chronic diseases like those having chronic renal failure, inflammatory bowel disease, and celiac disease. In addition, girls in their teens and toddlers are also more prone to this.[11] The most common cause of IDA in infants and young children is prolonged breast feeding in the absence of iron supplementation or excessive consumption of cow's milk and improper and inadequate weaning.[12] Depleted iron stores & microcytic hypochromic anaemia are typical characteristics of iron deficiency anaemia.[13] Various oral iron preparations were traditionally used in the treatment of IDA in the form of ferrous gluconate, ferrous fumarate, ferrous ascorbate& ferrous sulphate.[11]

Oral iron therapy is the first line treatment for children with IDA.[14] But intravenous (IV) iron therapy can be used in situations where the anaemic child is poorly compliant to oral iron therapy. Failure to respond to oral iron therapy can be due to malabsorption or lower compliance rates as a result of lack of commitment, poverty, prolonged treatment, decreased tolerability or gastro-intestinal upsets.

Although a lot of literature is available on oral iron therapy but material on intravenous iron therapy in children, especially in Pakistan is scarce.

So, objective of our study is to assess the effectiveness and safety of intravenous iron therapy in children with IDA refractory to oral iron.

MATERIAL AND METHODS

This cross-sectional quantitative analytical, multi-center study was conducted in the paediatric departments of three hospitals of Pakistan, including Allama Iqbal Memorial Teaching Hospital Sialkot, Saad Hospital Daska and Al-Noor Hospital Pasroor from October 2019 to September 2020. Ethical approval of this study was taken from Research ethics committee of Allama Iqbal Memorial Teaching Hospital Sialkot on 4th January 2021 with reference to letter No.47/REC/KMSMC. Written, informed consent was taken from parents/guardian before enrolling their anaemic children in the study.

The diagnosis of IDA was made by haemoglobin below 2SD of normal for the age and sex, along with serum ferritin levels of less than 16 ng/ml and red blood cell distribution width >15%.[15] A CRP level was done along with serum ferritin to rule out any inflammation. Any patient with raised CRP was not included in the study. Poor compliance to oral iron therapy was defined as any child diagnosed with IDA in which haemoglobin level is not raised to ≥1g/dL after 14 days of oral iron polymaltose complex at a dose of 4-6mg/kg/day of elemental iron in 2 divided doses.[16]

The sample size was calculated using WHO software "Sample Size Determination in Health Studies", keeping 80% power, 5% margin of error and considering outcome like increase in haemoglobin concentration, i.e., mean difference was -4.8 (reference attached), suggest to enrol n=6 patients for study. As the sample size was low for clinical significance so we enrolled eligible patients during study.[17]

We enrolled 114 children of both genders from 12–60 months of life diagnosed with IDA who were not responding to adequately prescribed oral iron therapy for 14 days. But 24 children did not return for follow up visits. The children whose parents/guardians did not give consent and those with chronic diseases like chronic kidney disease, congenital heart diseases, immune deficiencies, malignancies, syndromes and malabsorption were excluded from the study. So, 90 children were left in the end, participating in the study.

Total and absolute dosage of iron was calculated by using this formula.[18]

Total dosage of iron = (required Hb - observed Hb) x 80 ml x body weight x 0.034

Absolute dosage = total iron + 20% of total iron dosage

Blood volume of 80 ml/kg was used with the correction factor of 0.034 to build the iron stores. Absolute dosage of iron was divided in 2 doses administered over two consecutive days. Each IV iron dose was diluted in 100 ml normal saline in micro-burette and was infused over two hours. The initial infusion rate was 25 drops/min for first 20 minutes to observe for any adverse effects and gradually the infusion rate was increased to 50 drops/min to complete the infusion over two hours. Any adverse event during and 1 hour after infusion was also noted. Patients were followed up at two weeks and four weeks to check for haemoglobin level. For statistical analysis SPSS version 25 was used. Paired sample test and analysis of variance were used. $p<0.05$ was considered significant.

RESULTS

Of the 90 enrolled children 47 (52.2%) were males while 43 (47.8%) were females. Demographic variables and clinical characteristics are shown in Table I. The mean age of the participants was 23.1±10.73 months. The reasons for failure of oral iron supplementation were frequent diarrheal episodes on oral iron therapy (15.5%), refusal to oral iron due to bad taste and smell (35.6%) and non-compliant behaviour of the mothers (48.9%). The mean ferritin level before IV therapy was 3.75±2.53 ng/ml, whereas mean haemoglobin was 5.92±1.31 g/dl. After the IV iron was administered, a rise in mean haemoglobin level of 8.38±1.09 g/dl and 9.74±0.88 g/dl was observed at 2 weeks and 4 weeks post-therapy respectively (Figure-1). Paired t-test showed a statistically significant increase in mean haemoglobin (p-value <0.01) after parenteral iron therapy.

Only 3 (3.3%) patients developed fever and 2 (2.2%) patients experienced urticaria. None of the treated children experienced anaphylaxis, abdominal pain, nausea, constipation, diarrhoea or any other side effects that have been previously reported in the literature.

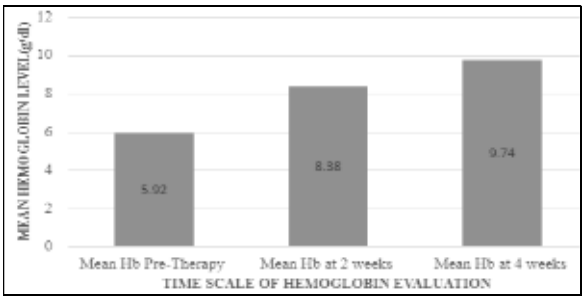

Figure-1: Rise in mean haemoglobin level, pre and post IV iron therapy

Table-1: Demographic and Laboratory characteristics of study participants

Variables	Number (%)
Gender	
Males	47 (52.2)
Females	43 (47.8)
Age(months) ± SD	23.1±10.73
Mean Ferritin level at diagnosis (ng/ml) ±SD	3.75±2.53
Mean haemoglobin Pre-therapy ± SD	5.92±1.31
Mean haemoglobin at 2-weeks post-therapy ±SD	8.38±1.09
Mean haemoglobin at 4-week post-therapy ±SD	9.74±0.89
Reason For Oral Treatment Failure	
Diarrhoea	14 (15.5)
Refusal	32 (35.6)
Non-Adherence	44 (48.9)
Adverse Effects	
Yes	5 (5.5)
No	85 (94.5)

DISCUSSION

The role of Intravenous (IV) iron therapy in paediatric population is debatable and there is lack of sufficient data regarding the safety of IV iron therapy in IDA.

We used an IV iron sucrose preparation which is approved by Food and Drug Administration of the United States and are associated with reduced risks of the hypersensitivity reactions [18]. Anaemia improved dramatically after intravenous iron infusions, with constant rise in haemoglobin levels.

Pinks V *et al*.[19] and Akin M *et al*.[18] also have similar studies with a bit different age groups as compared to our study population (average age 6year &7months and 46.9±61.5 months respectively). The mean baseline ferritin level of our study population was 3.77±2.83ng/ml. A study done by Akin M *et al*.[18] also showed similar baseline serum ferritin level (3.2±2.9ng/ml). We could not repeat the serum ferritin level at 2 or 4 weeks due to resource limitation.

The mean haemoglobin of our patients before treatment was 5.9±1.3g/dL which was raised to 8.4±1.1 g/dl (mean rise in Hb was 2.5 g/dL), two weeks after iron therapy. Another study by Pinsk V *et al*.[19] has also showed the similar results (baseline Hb was 7.43g/dl which was increased to 9.27g/dl at 2 weeks, the mean rise in Hb was 1.84). Four weeks after therapy the mean haemoglobin of our children was raised to 9.7±0.9g/dl (3.8 g/dL rise). Another study done by Akin M *et al*.[18] also showed a comparable rise at 4 weeks of therapy (baseline Hb was 7.9±1.2g/dl, at 4 weeks it was 10.6±1.5g/dl and rise in Hb was 2.7g/dl.).[19]

A study by Sabe R *et al*.[20] conducted on children and adolescents of inflammatory bowel disease with iron deficiency anaemia showed significant improvement in mean Hb level (baseline mean Hb was 9.1±1.4 which increased to 11.9±1.8 after 12 weeks of administration of intravenous iron sucrose). Similar to our study the rise in Hb level was significant but in contrast to our study they repeated the Hb level after 12 weeks while we repeated at 2 and 4 weeks after IV administration of iron.

Similar to our study IV iron was found to cause significant rise in mean Hb level in children with iron deficiency anaemia (from baseline mean Hb of 7.37±0.44g/dl to 9.47±0.47g/dl after 6 weeks of treatment) in a study done by Nazir F *et al*.[21] However, this study was done on malnourished children only.

The efficacy of IV iron observed in our study is also comparable to the efficacy of IV iron observed in anaemic pregnant women in a study done by Haldar P *et al*[22] (the mean rise in mean Hb level was 1.76g/dl at 4 weeks of IV iron administration).

The only adverse effects documented were fever and urticaria in our study. No serious side effects were reported. Other studies by Siddiqui Kaneva K *et al*.[23], Manatadakis E *et al*.[24] and Nestor JA *et al*.[25] also didn't show any serious adverse effects of IV administration. In a study by Zaman S *et al*.[26] mild rash and shivering in a few patients were observed. Whereas, in another study by Kaneva K *et al*.[23] the adverse effects observed were cough and wheezing.

Limitations:

Limitations of our study are that it is confined to a specified region, we did not repeat serum ferritin levels due to resource limitations and we did not follow-up the patients further after 4 weeks post therapy.

Although this study shows very encouraging results of IV iron therapy in children with IDA who remained non-compliant to oral iron treatment but results cannot be generalized due to small number of study participants. Further studies on a larger scale are needed to conclude whether the intravenous iron should be used as a first line therapy in paediatric population especially in situations where rapid rise in haemoglobin level is required.

CONCLUSION

Intravenous iron is safe and effective way to rapidly increase the haemoglobin levels in children with iron deficiency anaemia poorly compliant to oral iron therapy.

Conflict of interest: The authors declare no conflict of interest.

Sources of financial assistance: None to declare

AUTHORS' CONTRIBUTION

MMAB, SB, TA: Literature search, concept of study, data collection, write-up, proof reading. MR, SB, OA, SZ: Data collection, analysis.

REFERENCES

1. da Silva Lopes K, Yamaji N, Rahman MO, Suto M, Takemoto Y, Garcia-Casal MN, *et al*. Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews. Cochrane Database Syst Rev 2021;9(9):CD013092.
2. Engle-Stone R, Aaron GJ, Huang J, Wirth JP, Namaste SM, Williams AM, *et al*. Predictors of anemia in preschool children: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr 2017;106(Suppl 1):S402–15.
3. Jamnok J, Sanchaisuriya K, Sanchaisuriya P, Fucharoen G, Fucharoen S, Ahmed F. Factors associated with anaemia and iron deficiency among women of reproductive age in Northeast Thailand: a cross-sectional study. BMC Public Health 2020;20(1):102.
4. Owaidah T, Al-Numair N, Al-Suliman A, Zolaly M, Hasanato R, Al Zahrani F, *et al*. Iron Deficiency and Iron Deficiency Anemia Are Common Epidemiological Conditions in Saudi Arabia: Report of the National Epidemiological Survey. Anemia 2020;2020:6642568.
5. Clark KM, Li M, Zhu B, Liang F, Shao J, Zhang Y, Ji C, *et al*. Breastfeeding, mixed, or formula feeding at 9 months of age and the prevalence of iron deficiency and iron deficiency anemia in two cohorts of infants in China. J Pediatr 2017;181:56–61.
6. 6Abu-Ouf NM, Jan MM. The impact of maternal iron deficiency and iron deficiency anemia on child's health. Saudi Med J 2015;36(2):146–9.
7. Kumar D, Qureshi ZN, Albadwawi MS. Iron deficiency anemia in infants of Hatta suburb-UAE. Int Arch Nurs Health Care 2019;5:121.
8. DeLoughery TG. Safety of oral and intravenous iron. Acta Haematol 2019;142(1):8–12.
9. Carsley S, Fu R, Borkhoff CM, Reid N, Baginska E, Birken CS, *et al*. Iron deficiency screening for children at 18 months: a cost-utility analysis. CMAJ Open 2019;7(4):E689–98.
10. Moraleda C, Rabinovich NR, Menéndez C. Are infants less than 6 months of age a neglected group for anemia prevention in low-income countries? Am J Trop Med Hyg 2018;98(3):647–9.
11. Mantadakis E. Advances in pediatric intravenous iron therapy. Pediatr Blood Cancer 2016;63(1):11–6.
12. Powers JM, Buchanan GR, Adix L, Zhang S, Gao A, McCavit TL. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: a randomized clinical trial. JAMA 2017;317(22):2297–304.
13. Lanzkowsky P. Iron-deficiency anemia. In: Lanzkowsky's Manual of Pediatric Hematology and Oncology: Elsevier, 2016; p.69–83.
14. Powers JM, Shamoun M, McCavit TL, Adix L, Buchanan GR. Intravenous ferric carboxymaltose in children with iron deficiency anemia WHO respond poorly to oral iron. 2017;180:212–6.
15. Miniero R, Talarico V, Galati MC, Giancotti L, Saracco P, Raiola G. Iron Deficiency and Iron Deficiency Anemia in Children. InIron Deficiency Anemia; IntechOpen: London, UK. 2019; p.23–38.
16. Okam MM, Koch TA, Tran MH. Iron supplementation, response in iron-deficiency anemia: analysis of five trials. Am J Med 2017;130(8):991–e1.
17. Mantadakis E, Tsouvala E, Xanthopoulou V, Chatzimichael A. Intravenous iron sucrose for children with iron deficiency anemia: a single institution study. World J Pediatr 2016;12(1):109–13.
18. Akin M, Sarbay H, Guler S, Balci YI, Polat A. Response to parenteral iron therapy distinguish unexplained refractory iron deficiency anemia from iron-refractory iron deficiency anemia. Int J Lab Hematol 2016;38(2):167–71.
19. Pinsk V, Levy J, Moser DA, Yerushalmi B, Kapelushnik J. Efficacy and safety of intravenous iron sucrose therapy in a group of children with iron deficiency anemia. Isr Med Assoc 2008;10(5):335–81.
20. Sabe R, Vatsayan A, Mahran A, Khalili AS, Ahuja S, Sferra TJ. Safety and Efficacy of Intravenous Iron Sucrose for Iron-Deficiency Anemia in Children and Adolescents with Inflammatory Bowel Disease. Glob Pediatr Health 2019;6:2333794X19870981.
21. Nazir F, Khurshid A, Talib MA. Intravenous iron sucrose in malnourished children with iron deficiency anemia. Prof Med J 2020;27(9):1867–71.
22. Haldar P, Kant S, Yadav V, Majhi J, Malhotra S, Kaur R, *et al*. Effect of intravenous iron sucrose on hemoglobin level, when administered in a standard-dose, to anemic pregnant women in rural Northern India. J Family Med Prim Care 2018;7(4):762–8.
23. Kaneva K, Chow E, Rosenfield CG, Kelly MJ. Intravenous Iron Sucrose for Children with Iron Deficiency Anemia. J Pediatr Hematol Oncol 2017;39(5):e259–62.
24. Mantadakis E. Intravenous iron: safe and underutilized in children. Pediatr Blood Cancer 2018;65(6):e27016.
25. Nestor JA, Afridi FA, Suarez R, Karem JB, Hardiman M, Hunter K, *et al*. Intravenous Iron Infusions in Pediatric Patients: A Single Institution Assessment of Efficacy and Adverse Effects of IV Iron Infusions. Blood 2019;134(Suppl_1):5872.
26. Zaman S, Shah SA, Jehanzeb K, Sabir S, Rashid HU, Haq ZU. Effect of intravenous iron therapy on serum ferritin and haemogobin levels in children reporting with iron defeciency anaemia. Pak Armed Forces Med J 2020;70(5):1344–48.

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