EFFECT OF INTRAVENOUS IRON THERAPY ON SERUM FERRITIN AND HAEMOGOBIN LEVELS IN CHILDREN REPORTING WITH IRON DEFECIENCY ANAEMIA

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ABSTRACT

Objective: To evaluate the effect of intravenous Iron therapy on serum Ferritin and Haemoglobin levels in children with iron deficiency anaemia.
Study Design: Cross sectional study.
Place and Duration of Study: Combined Military Hospital (CMH), Quetta, from Aug 2015 to Jul 2017.
Methodology: Patients of either sex with age 1 to 12 years with iron deficiency anemia were included in the study. Sampling technique was Consecutive non-probability purposive sampling. Iron deficiency anemia was diagnosed on the basis of mean corpuscular volume (MCV), Hemoglobin (hb) concentration and serum ferritin. Intravenous iron therapy was given to all patients included in the study. Patients were followed up after 4 weeks. Paired t-test was applied for pre and post therapy HB and serum Ferritin. A *p*-value ≤0.05 was considered significant.
Results: Total number of patients included in the study was 55. Out of total patients male were 35 (64%) and female were 20 (36%). Mean age of patients was 2.48 ± 1.89 years. Pre therapy Hb and serum ferritin were 8.13 ± 1.96 g/dl and 8.87 ± 10.24, respectively. Post therapy HB and serum ferritin were 11.06 ± 93 g/dl and 52.60 ± 28.61 respectively. When paired t test was applied, the *p*-value was found statistically significant <0.05.
Conclusion: Intravenous iron therapy effectively improved serum ferritin and Hb concentration in patients with iron deficiency anemia.

Keywords: Hemoglobin, Iron deficiency anemia, Mean corpuscular volume, Serum ferritin.

INTRODUCTION

Worldwide about 40% of children are anemic[1]. Anemia in children is defined as Hb <11g/dl[2]. According to WHO report about 40% pregnant women and 50% children in developing countries are anemic[3]. In our setup anemia is mostly due to mal-nutrition and iron deficiency is the most common cause. Even in countries like UK and USA, about 10% children of age 1 to 2 years suffer from iron deficiency anemia and about 30% are iron deficient. In some high-risk population like low birth weight and premature infants, iron deficiency anemia is more prevalent[4]. In recent years much more attention has been paid to treatment of iron deficiency anemia in children. The reason being if left untreated, it can cause long term permanent detrimental effects on cognition, school performance, immune system and neurological function[5]. Children with IDA are more prone to stroke[6]. In some rare instances children with iron deficiency anemia may land in emergency department with life threatening conditions like congestive heart failure and severe respiratory distress thus may need admission to intensive care unit[4].

Different modalities of treatment exist for treating iron deficiency anemia, each having its advantages and disadvantages[7]. Oral iron is cheap and effective way of treating iron deficiency anemia but in some patients, oral iron cannot be tolerated like in case of chronic diarrhea and low compliance to treatment. In such cases iron has to be submitted through parental route[8]. Parental iron supplementation provides faster replenishment of iron supplementation with

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rapid rise in hemoglobin and is now becoming more popular. Different safe and effective iron preparations are available[9]. In the past iron dextran, a high molecular weight iron preparation, was frequently used in patient on hemodialysis and those with iron deficiency anemia, but due to its serious adverse effects, particularly anaphylaxis reactions, its use has almost been abandoned. New iron preparations are now available for parenteral uses which are safer than and as effective as HMW dextran. The new preparations available include low molecular weight dextran, ferumoxytol, iron sucrose and ferric gluconate[10]. Iron sucrose is now FDA approved in patients on hemodialysis. As compared to iron dextran, iron sucrose is associated with less adverse effects.

Experience with iron therapy is over hundreds ofyearsold[11]. Most of the trial of intravenous iron has been carried out among oncology patients, on dialysis, and suffering from inflammatory bowel disease. Trials of intravenous iron for iron deficiency anemia are few. The response to intravenous iron is so dramatic that it is now being advised that the claim 'that oral iron should be used as first line therapy for iron deficiency anemia' should be reconsidered. There are no prospective studies on long term iron toxicities. The only serious fear is that iron therapy prone patients to infection as iron is pro oxidant. But increased survival has been documented with its use[12]. Adverse events have mostly been observed when the dose is not appropriate i.e. given in high dosage than recommended and when the dose is infused rapidly. Adverse reactions observed in such cases are drop in blood pressure, body aches and vomiting. Appropriate dose when infused slowly, minimal adverse effects are observed. Recent study showed that there is no increased risk of infection with intravenous iron[13].

The rationale behind our study was that if intravenous iron sucrose proved to be effective in treating iron deficiency anemia, then it would be a better alternative for children who cannot tolerate oral iron or those with chronic diarrhea.

METHODOLOGY

This cross-sectional study was carried in the pediatric department of Combined Military Hospital, Quetta. The study period extended from August 2015 to July 2017. Study was conducted after taking approval from hospital research ethics committee. Sample size was calculated using World Health Organization software for sample size calculation which was 96, where anticipated population proportion was 70%[14], confidence interval is 95% and absolute precision required was 5% and sampling technique used was non probability consecutive sampling. The purpose of the study was explained to the parents of the patients. They were told that all information would be kept confidential and that the study was purely done for research purposes. Operational definitions used were:

Anemia was defined as Hb less than 10 g/dl. Iron deficiency anemia: Child with anemia having MCV <70fl and Serum Ferritin <20ng/ml. Pica A craving for something that is not normally regarded as nutritive, such as dirt, clay, paper or chalk. Worm Infestation Any disease or disorder usually of the intestine, characterized by infestation with parasitic worms.

Feeding type of milk used for feeding was discussed which includes Cow's milk, buffalo milk or formula feed. Duration of exclusive breast feeding and time of initiating weaning was asked from parents.

Patients with Iron deficiency anemia of ages 1 to 12 years of either gender, non responsive to oral iron therapy, history of gastrointestinal adverse effects with oral iron therapy or those who had noncompliance with oral iron were included in our study. Children with chronic renal failure, liver diseases or cardiac disease and children who did not report after intravenous iron therapy for follow up and children with any acute infection or who are C Reactive Protein positive were excluded from the study. All patients were subjected to detailed history which included duration of breast feeding, time of initiating weaning, history of pica and worm

infestation, was taken along with detailed examination. Blood samples of all patients were collected for blood complete picture (which included Hb, platelets, total leucocyte count, differential leucocyte count and MCV), serum ferritin and C-reactive protein to rule out and acute infection. All thepatients were admitted in the hospital for intravenous iron therapy. During intravenous iron the patients were closely observed. Senior pediatric trainee was detailed to observe vital signs and to provide appropriate and timely treatment if any adverse event occurs. After iron therapy the patients were observed for 4 hours and if stable were discharged with follow up advised after 4 weeks. Of the total 96 patients only 55 patients reported for follow up and their complete blood count and serum ferritin were advised and documented. Except for mild rash and shivering in a few patients no adverse event was observed. Standard dose per kg body of iron was diluted in normal saline and was infused slowly over 4 hours. All the patients were given a test dose of 0.5 ml diluted in 10ml normal saline.

All the collected data was analyzed in SPSS version 23. Mean ± SD was calculated for numerical variables like age (in years) of the children, serum hemoglobin and Ferritin levels. Frequencies and percentages were calculated for categorical variables like gender. Chi square test was applied on history of pica, worm infestation and type of milk used for feeding. Paired Sample "t" test was applied to find out the significant difference between the pre and post treatment Hb and serum ferritin levels. A *p*-value ≤0.05 was considered as significant.

RESULTS

Total number of patients in our study was 96, only 55 reportedback for follow up. Out of total patients 35 (64%) were male and 15 (36%) were female. Mean age of patients was 2.48 ± 1.89 years. History of pica was positive in 18 (33%) patients, history of worm infestation was positive in 7 (13%) patients. Frequency of milk other than mother feed was cow milk in 29 (53%), formula milk was taken by 20 (36%) and buffalo milk by 3 (5%) patients. Mean duration of exclusively breast feeding was 2.75 ± 2.40 months. Time of weaning started was 6.45 ± 1.08 (Mean ± SD) months. Pre therapy Hb and serum ferritin were 8.13 ± 1.96 g/dl and 8.87 ± 10.24ng/ml, respectively. Post therapy Hb and serum ferritin were 11.06 ± 93 g/dl and 52.60 ± 28.61ng/ml, respectively. Paired t test was applied and it was less than 0.001. The results are given in table-II.

Table-I: Descriptive statistics of study population.

n=55	Mean ± SD
Age (years)	2.58 ± 1.89
Pre Treatment Hb (gm/dl)	8.13 ± 1.19
Post Treatment Hb (gm/dl)	11.06 ± 0.93
Pre Treatment S. Ferritin (ng/ml)	8.87 ± 10.24
Post Treatment S. Ferritin (ng/ml)	52.60 ± 28.61
Exclusively breast feeding duration (years)	2.75 ± 2.40
Time of weaning started (months)	6.45 ± 1.08

Table-II: Paired sample t test for Pre and Post therapy Hb and S.Ferritin.

	Paired Differences (Mean ± SD)	*p*-value
Pair-1: Post treatment Hb (gm/dl) - Pre treatment Hb (gm/dl)	2.92 ± 1.18	<0.001
Pair-2: Post treatment Serum Ferritin-Pre treatment Serum Ferritin	43.72 ± 23.71	<0.001

Table-III: Post stratification Chi Square data.

Parameters	Male	Female	*p*-value
History of Pica			
Present	14 (40%)	4 (20%)	0.128
Absent	21 (60%)	16 (80%)	
Worm Infestation			
Present	4 (11.5%)	3 (15%)	0.702
Absent	31 (88.5%)	17 (85%)	
Type of Milk			
Formula	14 (40%)	6 (30%)	0.390
Cow	18 (51.5%)	11 (55%)	
Buffalo	3 (8.5%)	3 (15%)	

DISCUSSION

Iron deficiency anemia is one of the most common causes of anemia among children. Its treatment includes oral/IV iron replacement along with adequate dietary advice to the parents. The problem with oral iron therapy

observed in most of the cases is compliance, its gastric side effects which occur in up to 60% of the patients. The problem was resolved by intravenous iron therapy which is available in different formulation. The initial intravenous iron therapy was started with high molecular weight iron dextran. It was banned in the early nineties due to its serious adverse effects. With the availability of low molecular weight iron dextran, the popularity of intravenous iron therapy again increased. Intravenous iron is preferred since administered through intramuscular route may cause severe pain, results in skin discoloration and israrely associated with sarcomas[12]. In our study we did not observe any adverse effects. The reason may be the small sample size partially because of the fact that many patients failed to follow up. The pharmacokinetics of all the formulation is almost same. After administration the free iron is stored as ferritin. Of all the available formulations, iron sucrose is the approved drug for intravenous administration in both UK and USA[15]. In our study too, we used iron sucrose and the route of administration chosen was intravenous due the already mentioned reasons.

Our study showed that intravenous iron sucrose effective in raising Hb and serum ferritin level. Other studies have also showed similar results. Mantadakis *et al* carried out a study in which they included 12 patients. All the patients were with iron deficiency anemia and they received up to 3 doses of intravenous iron sucrose. The patients were reviewed after 4 to 6 weeks and all showed improvement in their Hb concentration, rising to normal value. Iron sucrose was effective in raising the hemoglobin concentration to normal in all patients with IDA, i.e., from 7.6 ± 2.38 g/dL to 12.4 ± 0.64 g/dL, within 31-42 days after the first infusion. They also observed minimal adverse reaction at injection site and alteration in taste[16]. In contrast patients in our study reported patients were 55, and all received 2 doses of intravenous iron sucrose. Patients were reviewed after 4 weeks and though Hb of all patients was not raised to normal limits but still statistically significant rise was observed. Nazir *et al* treated iron deficiency anemia with IV iron sucrose effectively. The mean pretreatment Hb in their patients was 7.85 ± 0.78 gm/dl and it raised to 10.29 ± 0.89 gm/dl post treatment. The difference was statistically significant with *p*-value less than 0.001[17]. But as compared to our study the number of patients included in their study was 142, a figure much higher than our study. The problem in our study was that most of the patients lost follow up. The study population was mostly from army set up and the reason of loss of follow up is mostly their postings. Another Indian study recruited 50 patients with iron deficiency anemia and transfused them with intravenous iron sucrose. They diagnosed iron deficiency anemia on the basis of Hb concentration and red blood cell indices whereas we did serum ferritin in addition to red cell indices. Like our study they also found iron sucrose effective in raising Hb concentration in patients with iron deficiency anemia.Their study demonstrated that administration of iron sucrose caused increase in all the estimated hematological parameters. On the 30th day after treatment, average Hb level, hematocrit, RBC count increased from 6.95 ± 0.72 g/dl to 12.10 ± 0.69 g/dl, 21.19 ± 2.33% to 37.33 ± 2.45%, 3.48 ± 0.37x10^6 cell/cu.mm to 5.56 ± 0.41 x 10^6 cell/cu.mm, respectively[7]. Other studies have also claimed iron sucrose to be effective in treating Iron deficiency anemia where the improvement in Serum Ferritin values and rise in Hb levels was revealed, *p*-value <0.001. Pinsk *et al* concluded that Serum ferritin level prior to therapy was low in all patients: mean 3.5 nmole/L (SD = 7.55), (normal range 16–250 nmole/L). The serum ferritin level rose to a mean of 60 nmole/L (SD = 47.73) after 14 days (p<0.000)[18] similar to our study, Crary *et al* compared two groups of children for rise in Haemoglobin after oral and IV iron therapy. The response to oral iron was determined by the difference in the hemoglobin concentration just prior to oral iron therapy and immediately prior to switching to iron sucrose. The response to IV iron sucrose was then measured by the difference between hemoglobin value just prior to starting iron sucrose and either

the most recent value obtained after IV iron sucrose. IV iron sucrose was effective at raising the hemoglobin concentration and was superior to oral iron in the children refractory to oral iron with a median hemoglobin rise of 1.9–3.1g/dl (p<0.001 and p=0.04, respectively)[19]. Our study included serum Ferritin as well as change in Haemoglobin after intravenous Iron therapy.

CONCLUSION

Intravenous iron sucrose was found an effective and safe medication for iron deficiency anemia. It resulted in a significant rise in Hb in patients with iron deficiency anemia. Our study was a single centered small study so before it should be recommended as first line therapy for iron deficiency anemia, multi centered large trial are required.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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