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Original Article

Obstetrics and Gynaecology Section

Evaluation of Efficacy of Intravenous Iron Sucrose in Management of Adolescent Iron Deficiency Anaemia

SAUBHAGYA KUMAR JENA[1], ARATI MALLICK[2], SUSHREE SANGEETA ROUT[3]

ABSTRACT

Introduction: Worldwide, most common nutritional deficiency anaemia is iron deficiency anaemia. Anaemia in adolescent girls is defined as blood haemoglobin (Hb) level <12g/dL. The highest prevalence seen in ages of 14-19 years, more than 50% girls of this age are anaemic. It affects both physical endurance and cognitive performance in adolescent. Adolescent anaemia if not corrected at proper time, will attribute to the high maternal mortality rate, higher incidence of low birth weight babies and high perinatal mortality rates.

Aim: To establish the efficacy and safety of intravenous iron sucrose and to compare with oral iron ascorbate in management of iron deficiency anaemia in adolescent girls.

Materials and Methods: It is a prospective, interventional, hospital based clinical study carried out in over 61 adolescent girls (10-19) years, having haemoglobin 8-<12 g/dL. Thirty girls were given intravenous iron sucrose and 31 girls were given oral ferrous sulphate. In intravenous group, 200-800 mg intravenous iron sucrose has been given in divided doses, 200 mg (per dose) diluted in 200 ml of normal saline on alternate day whereas in oral group, 200 mg ferrous sulphate tablet given orally, twice daily for three weeks. Data was collected after four week for haemoglobin and Packed Cell Volume (PCV) estimation.

Results: A significant improvement of haemoglobin was observed with intravenous iron sucrose. The mean haemoglobin was increased from 9.9±0.94 gm/dL to 11.54±0.80 gm/dL after four weeks. Within a short span of four weeks, intravenous iron sucrose leads to a significant increase ($p<0.001$) in haemoglobin concentration of 1.6±0.83 g/dL compared to 0.89±0.48 g/dL increase in concentration of haemoglobin in oral iron sulphate group. Iron sucrose was very well tolerated. Only one out of 30 patients experienced headache and burning sensation at injection site. 20 (64.5%) girls in oral group complained of gastrointestinal side effects like nausea, dyspepsia and constipation compared to none in intravenous group.

Conclusion: Overall, intravenous iron sucrose therapy compared to oral iron ascorbate found to be very effective in treating mild to moderate anaemia in adolescent girls with negligible side effects and good safety profile.

Keywords: Adolescent anaemia, Adolescent girls, Haemoglobin, Packed cell volume

INTRODUCTION

Worldwide anaemia is arising as a major public health problem and ignored in both developed and developing countries. It is defined as blood haemoglobin level <12 g/dL in adolescents and adult women, <11 g/dL in pregnant women and <13 g/dL in adult men. The vulnerable are pregnant women, adolescents and pre-school children [1]. The incidence of iron deficiency was 9% and iron deficiency anaemia was 2% among American females between the ages 12 and 15 years; the respective values were 11 and three percent in girls between the ages of 16 and 19 years [2]. A study showed that 90% adolescent girls from 16 districts of India were anaemic and 7.1% had severe anaemia [3].

Adolescent girls are the main victim. In a family with limited resources, they are neglected, deprived of good food and education, utilized as an extra working hand to carry out household works. The pubertal growth spurt, menstrual blood loss often worsens the situation [4]. Iron deficiency anaemia cause reduced work capacity in adults, affect motor and mental development in children and adolescents, cognitive impairment in adolescent girls and fatigue in adult women [5-8].

Adolescent girls are more vulnerable to nutritional deficiencies because of the greater demand of nutrients due to physical and physiological changes [5]. After menarche, iron need increases because of menstrual blood loss, average 20 mg per month to as high as 58 mg [9]. Low dietary intake and poor bioavailability of iron consumed are another contributing factors. Over 70% of adolescent girls consume less than 50% Recommended Daily Allowance (RDA) of iron [10]. Majority of young married women conceive soon after marriage, because of social and family pressure. Increased demands of iron requirement in pregnancy due to physiological changes and increased demand by growing foetus, add on to the existing iron deficiency leading to anaemia [11].

A study estimated, approximately 25% of women in developing countries have their first child by 19 years of age and many more in the following years, thus making adolescence an important "preparatory period" for a healthy mother and infant [12]. Because, it is difficult to know when pregnancy will occur hence, maintaining adequate iron status throughout adolescence and young adulthood, will ensure the nutritional status and health of both current and future generation.

Maintaining adequate iron status during adolescent pregnancy is more challenging because the iron needs for pregnancy will be superadded with adolescent's rapid rate of growth [13]. Anaemia in adolescent girls results in low pre-pregnancy iron store and pregnancy is a very small time period to build the deficient iron stores required to meet the needs of the growing foetus. Not only anaemia directly affects maternal survival, it also leads to complications such as postpartum haemorrhage. An Indian study found that women who has not received iron-supplementation during pregnancy were more likely to experience postpartum haemorrhage, which is the leading cause of maternal mortality [14]. Anaemia during pregnancy also increases risk of low-birth weight, premature delivery, iron deficiency and anaemia later in infancy [15].

In a randomized controlled trial on iron-supplementation in iron-deficient adolescent girls who had not yet become anaemic show that, girls receiving iron supplements performed better on a test

of verbal learning and memory than placebo [16]. Another study on anaemia in adolescent children of United States showed that those having iron deficiency had twice the risk of scoring below average in mathematics than children with adequate iron status, though there was no effect on verbal skills [17]. Studies involving iron supplementation to anaemic adolescent children, showed an increase in weight and height gain among supplemented children, particularly during the earlier part of adolescence (10-14) years in comparison to placebo [18]. Hence, investigating and preventing anaemia during adolescence is critical for adolescent girls themselves as well as for the survival, growth and development of their children later in life.

As per World Health Organization (WHO) global database on iron deficiency anaemia, timely treatment can restore personal health and raise national productivity levels by as much as 20% [1]. Treatment of iron deficiency anaemia comprises oral iron, Parenteral iron and blood transfusion in severe cases. Although, traditionally oral iron therapy is the recommended treatment for iron deficiency anaemia, oral iron often associated with side effects, poor compliance and takes a long time to correct anaemia. Parenteral preparations like iron dextran, iron sorbitol are associated with anaphylactic reactions, on the other hand blood transfusions are associated with cross reactions and viral infections. Recently, there has been an increasing interest on alternative therapeutic options like intravenous iron sucrose and human recombinant erythropoietin. Iron sucrose is widely used, very safe and effective with minor adverse effects like flushing of the face and burning at the injection site (0.5 %) of cases, metallic taste [19]. Slow release of iron from the iron sucrose complex and low allergenicity of sucrose, results in its high tolerance level. Iron sucrose complex has high availability for erythropoeisis, less renal excretion, less tissue accumulation and lower toxicity [20].

Very few studies have been conducted to measure with reasonable precision the rates with which these iron preparations can correct iron deficiency anaemia, even much fewer studies on adolescent anemia [3]. The present study was an attempt to compare the efficacy and safety of iron sucrose and oral iron for the treatment of iron deficiency anaemia in adolescent girls.

MATERIALS AND METHODS

This is a single centre, prospective, interventional, hospital based clinical study on determining the efficacy of intravenous iron sucrose over oral iron ascorbate in adolescent females having Iron Deficiency Anaemia, attending the outdoor of Department of Obstetrics and Gynaecology from June 2016 to December 2016.

Sixty one Adolescent females with age between 10 to 19 years with established iron deficiency anaemia, confirmed with Hb 8-12 g/dL and Peripheral blood smear features suggestive of iron deficiency anaemia were considered. Pregnancy, Chronic illness like tuberculosis and other type of anaemia were excluded. A voluntary written informed consent was obtained from each patient after explaining the benefit and harm of joining the study and freedom of withdrawing at any moment they would like to want. Study was conducted following ICMR's ethical guidelines for biomedical research on human subjects (2006) after getting written approval of the Institutional Ethics Committee [IEC Proposal: T/IM-NF/O and G/16/11] .

After obtaining informed written consent, detailed clinical examination, laboratory investigations such as Hb, PCV was done at baseline and at the end of therapy. Patients fulfilling the inclusion criteria were included in either of two groups. Excluding lost to follow-up, at the end intravenous group constituted 30 patient and oral group 31 patients.

Oral group: 200 mg ferrous sulphate oral tablets, each containing 60 mg elemental iron was given twice daily for three weeks. Intravenous group: Iron sucrose (Injection Orofer S, Emcure Pharmacueticals Limited, India) was used in the study. Total dose of intravenous iron was calculated using following formula.

Formula for total iron dose (mg)=2.4×(target Hb-actual Hb)×weight (kg).

Total cumulative dose was divided and given every alternate days until desired dose was achieved. Intravenous iron sucrose 200 mg in 250 ml of normal saline/day after a test dose was administered. Subsequent doses given on alternate days without test dose. Minimum 200 mg/day and up to a maximum of 800 mg/week was administered.

Patients had free access to the investigators for reporting any adverse effects experienced by them. Adverse effect of intravenous iron sucrose was noted after test dose, during infusion, after completion of infusion. Both immediate and late complications if any noted, indirectly by patient complaint such as itching at injection site, breathlessness, red patches at injection site and monitoring patient vitals i.e. hypotension, tachycardia.

All patients follow-up after four weeks and haematological parameters like Hb and PCV were done, Clinical improvement in symptoms was assessed. Pre and post-treatment mean values of Hb, PCV were compared individually and between the two groups. Gastrointestinal disturbances such as nausea, vomiting, constipation, metallic taste, fever, pruritus at injection site, hypotension and local extravasation of drug or any anaphylactic reactions etc. were noted.

STATISTICAL ANALYSIS

Student t-test was used to compare demographic characteristics and baseline laboratory parameters of study groups. Comparison of means of continuous variables was done using two-sided paired t-test. Wilcoxon rank sum test and Fisher's exact test was used for categorical variables. Statistical analyses was performed using statistical software SPSS V.22 (IBM, NY USA) considering a significance level of $p<0.05$.

RESULTS

During the study period, total 334 adolescent girls attended Obstetrics and Gynaecology outdoor of our institution. A total of 112 patients were screened for recruitment. Forty four (44) patients were excluded as 28 patients did not meet the inclusion criteria and another 16 patients declined to participate. Total 68 adolescent patient with Iron Deficiency Anaemia (IDA) were finally recruited in this study time and follow up after four weeks. In follow up, we have lost seven patients and 61 patients were evaluated after drug therapy. Among 68 patients, intravenous group included total of 30 patients and oral group included total of 38 patients. After four weeks all 30 patients came for follow up in intravenous group but seven patients are lost to follow up in oral group.

As stated in [Table/Fig-1], out of total 61 patients, most of the patients i.e. 46 (75.4%) belonged to the age group of 15-19 years (Late Adolescents). Even in both the groups the late adolescent girls constituted major part. The mean age of the population was

Baseline Characteristics		IV Group(n=30)	Oral Group (n=31)	Total (n=61)
Age	10-14 yrs	8 (26.6%)	7 (22.6%)	15 (24.6%)
	15-19 yrs	22 (73.4%)	24 (77.4%)	46 (75.4%)
SES	Lower	8 (26.7%)	13 (42%)	21 (34.4%)
	Lower Middle	11 (36.7%)	9 (29%)	20 (32.7%)
	Middle	6 (20%)	4 (13%)	10 (16.4%)
	Upper Middle	1 (3.3%)	3 (9.6%)	4 (6.5%)
	Upper	4 (13.3%)	2 (6.4%)	6 (10%)
Education	Literate	25 (83.3%)	24 (77.4%)	49 (80.3%)
	Illiterate	5 (16.7%)	7 (22.6%)	12 (19.7%)
Demographic Distribution	Urban	8 (26.7%)	5 (16.1%)	13 (21.3%)
	Rural	22 (73.3%)	26 (83.9%)	48 (78.7%)

[Table/Fig-1]: Baseline demographic data.

(16.04±2.23) in intravenous group and (16.73±1.71) in oral group.

Socioeconomic status was calculated according to Modified BG Prasad's Socioeconomic status scale [21]. As stated in [Table/Fig-1], in both the groups most of the patients belonged to lower and lower middle class. Out of total 61 patients, majority i.e. 21 (34.4%) belonged to lower class and 20 (32.7%) patients belonged to lower middle class. About 19.7% of total study population i.e. 12 girls were illiterate, didn't attended the school at all. Demographic distribution as mentioned in [Table/Fig-1] showed 78.7% of total study population belonged to rural area.

The required iron dose varied depending upon index haemoglobin level and weight. The number of intravenous iron sucrose infusions per patient ranged from 1-4 doses, the individual doses ranged from 200–800 mg. Average iron requirement was 400±159 mg.

[Table/Fig-2] clearly demonstrates a significant improvement of clinical parameters i.e. Hb, PCV with intravenous iron sucrose where the mean Hb was increased from 9.9±0.94 gm/dL to 11.5±0.8 gm/dL after four weeks, the difference was 1.6±0.83 with p-value <0.001, which was clinically significant. On the other hand, in oral group mean Hb was increased from 10.56±0.79 gm/dL to 11.45±0.83 gm/dL and the mean difference was 0.89±0.48, with p-value <0.001.

According to [Table/Fig-2], similarly a significant improvement in PCV value seen in intravenous iron group, where the mean PCV was increased from 31.43±2.76 to 36.17±2.6 after four weeks, with a difference of 4.74±3.17 and p-value was <0.001, which was clinically significant. After four weeks mean PCV in oral group raised from 33.12±2.4 to 35.29±1.99 and the mean difference was 2.16±2.14 and p-value was 0.003.

Group	Parameters (Mean±SD)	Baseline	After four Months	Increase	p-value
IV	Haemoglobin	9.9±0.94	11.54±0.80	1.6±0.83	<0.001
	PCV	31.43±2.76	36.17±2.6	4.74±3.17	<0.001
Oral	Haemoglobin	10.56±0.79	11.45±0.84	0.89±0.48	0.001
	PCV	33.12±2.4	35.29±1.99	2.16±2.14	0.003

[Table/Fig-2]: Baseline clinical parameters and outcome after intervention (SD=Standard Deviation).

Out of 30 patients treated with iron sucrose, only one patient complained of headache and mild itching at injection site. Patient was fine after symptomatic treatment. However, in oral group 20 women (64.5%) complained of gastrointestinal side effects like nausea, dyspepsia and constipation they were not severe enough to affect the compliance. In this study there were seven dropouts in oral group and none in intravenous group. Gastrointestinal side effects were not seen in women on intravenous iron therapy. Compliance was 79% in oral group and 100% in intravenous group.

DISCUSSION

Iron Deficiency Anaemia (IDA) in adolescent girls affect their growth, development, physical fitness and future work productivity, hence, it should be treated early and effectively. In our study, most of the patients i.e. 46 (75.4%) belong to the age group of 15-19 years (Late Adolescents). Mean age of the population was (16.04±2.23) in intravenous group and (16.73±1.71) in oral group. It clearly indicates that IDA was more common in older adolescents and it may be due to increased requirement of iron during second spurt of growth. The result was supported by a micronutrient survey in which 72-80% younger (12-14 years) adolescent and 74-84% older adolescents (15-17 years) were found to have IDA [10].

A significant improvement of anaemia was observed with intravenous iron sucrose. Intravenous iron lead to a significant increase (p<0.001) in Hb concentration of 1.6±0.83 g/dL within four weeks only. On the other hand in oral group there was increase of 0.89±0.48 g/dL only. The difference in Hb between both the groups was statistically significant (p=0.001). Result was similar to study by Crary SE et al., which reviewed 38 children with IDA aged ≤18 years treated with intravenous iron sucrose, excluding those with renal insufficiency. Patients in all categories had a good response to the iron sucrose, with a median haemoglobin rise of 1.9-3.1 g/dL depending on the indication [22].

Mean Hb rise was also comparable to study by Mantadakis E et al., in which iron sucrose was effective in raising the Hb concentration to normal in all children 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. Injection site disorders in three cases and transient taste perversion in one case were the only side effects [23]. Akarsu S et al., evaluated its efficacy and safety in 62 children with IDA. They concluded that iron sucrose was effective for rapid correction of iron deficiency anaemia in children. The pre-treatment level of Hb rose from 7.9±1.2 g/dL to 11.4±1.1 g/dL three months after therapy. Mild side-effects were encountered in only eight patients (12.9%): facial rash in three, fever with irritability and flushing in three, urticaria in one, unusual food craving in one [24]. In a study on parenteral iron therapy in children with iron deficiency anaemia by Roganović J et al., a total of 76 intravenous iron infusions were administered to 12 children. Intravenous iron led to a significant increase (p<0.005) in Hb concentration of 2.7 g/dL within two months (range 0.4 to 5.4 g/dL). There was only one mild adverse reaction [25].

Severe systemic reactions after parenteral iron administration have been reported in the literature, with possible fatal outcome. Iron dextran has higher incidence of anaphylaxis compared to iron sucrose and iron gluconate [26]. Use of these preparations may rarely be associated with hypotension, flushing, abdominal pain, and nausea/vomiting. Therefore, caution is warranted with every dose of intravenous iron formulation [27]. Iron sucrose was very well tolerated. No infusion was associated with cardiovascular or respiratory complications. Only one patient experienced headache and Injection site disorders, i.e. burning that diminished with slower administration. Twenty (64.5%) girls in oral group had gastrointestinal complaints like nausea, dyspepsia and constipation. It was not seen in intravenous group. Compliance was 79% in oral group and 100% in intravenous group. Result was similar with study by Mantadakis E et al., where injection site disorders in three cases and transient taste perversion in one case were the only side effects [23]. A study by Perewusnyk G et al., over 400 women who received a total of 2000 ampoules of iron sucrose showed minor adverse effects including a metallic taste, flushing of the face and burning at the injection site in 0.5% cases only [19].

When analyzed across time it was found that intravenously administered iron sucrose group was significantly more likely to have higher Hb from baseline than those patients with orally administered iron at 4th week during the course of the study similar to other studies.

The observations and results presented here is of small population of 61 patients only. However, two factors are associated which limits the use of intravenous iron therapy, first is the cost compared with oral iron and second is the increase in hospital stay, but it is again linked to better patient compliance and faster recovery [28].

LIMITATION

The limitation was very small sample size and being conducted in single centre. The findings of this study can be confirmed by a multicentre, randomized, double-blind, large population based study.

CONCLUSION

Analysis of results of all the parameters of safety and efficacy indicate that intravenous iron sucrose therapy compared to oral iron ascorbate was very effective to treat mild to moderate anaemia in adolescent girls. It has a good safety and tolerability profile and negligible side effects.

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PARTICULARS OF CONTRIBUTORS:
1. Additional Professor and Head, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.
2. Senior Resident, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.
3. M.B.B.S Student, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Arati Mallick,
C/O Dr. B.K. Kuanar Gayatri Vihar, Chandi Chhak, Cuttack-753001, Odisha, India.
E-mail: draratimallick@gmail.com

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