Oral versus intravenous iron therapy in iron deficiency anemia: An observational study

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ABSTRACT

Background: Intravenous (IV) iron sucrose is claimed to have better safety profile and efficacy in treatment of iron deficiency anemia than conventional oral iron supplements. Aim: The aim of the study was to compare the efficacy and safety of IV iron therapy with oral iron supplements in iron deficiency anemia. Methods: An observational study was carried out by allocating 100 patients with baseline hemoglobin between 5 and 10 g/dL into two groups of oral iron and IV iron group. Hemoglobin and serum ferritin levels were measured at admission, on day 14 and on day 28. Adverse effect profile for each group was tabulated. Results: A total of 100 patients participated consisting of 37 males and 63 females. Baseline hemoglobin and serum ferritin for both groups were comparable. After initiation of therapy, hemoglobin in oral iron group raised from 6.45 (0.72) to 8.84 (0.47) on day 14 and to 9.69 (0.47) on day 28. Hemoglobin in IV iron group increased from 6.34 (0.86) to 10.52 (0.61) on day 14 and to 11.66 (0.84) on day 28. Serum ferritin in oral iron group increased from 8.3 (1.9) to 33.8 (1.29) on day 14 and to 43.61 (8.8) on day 28. Serum ferritin in IV iron group raised from 8.23 (4.64) to 148.23 (11.86) on day 14 but decreased to 115.76 (15.3) on day 28. The data were statistically significant for IV iron therapy on day 14 and day 28. Of 100 patients, 18 patients (12 in oral and 6 in IV iron groups) had adverse effects. Among the oral iron group, metallic taste and constipation were major side effects followed by heart burn and nausea. In the IV iron group, arthralgia (4 patients of 6) was the major side effect observed. One patient (of 6) in IV group had hypotension. Anaphylaxis was not observed in any patient in either group. Conclusion: IV iron therapy is effective and safe for management of iron deficiency anemia.

Keywords: Iron deficiency anemia, intravenous iron sucrose, oral ferrous sulfate

Introduction

Iron is a critical element in function of all cells of human body and takes major role in oxygen transport as a part of hemoglobin (Hb). Iron deficiency anemia is worldwide health problem and also is the commonest form of nutritional deficiency. It occurs as a late manifestation of prolonged negative iron balance, which can be due to nutritional deficiency, chronic blood loss, impaired iron absorption from gastrointestinal tract, multiple pregnancy, or worm infestations.

Historically the oral route of administration of iron was given much attention but the effectiveness of oral formulations are compromised by poor absorption, poor compliance and side effects. Blood transfusions for iron deficiency anemia depend upon severity of anemia. The hemoglobin level at which blood transfusion to be given varies from clinicians to clinicians with a possibility of unnecessary transfusions. There are also

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chances of mismatched transfusions, infections particularly HIV and hepatitis, and transfusion related acute lung injury which are difficult to handle. Therefore searching an alternative to raise hemoglobin in iron deficiency anemia, we can think of parenteral iron formulations. Early parenteral formulations are associated with much adverse reactions and are withdrawn from many countries. They were surpassed with introduction of iron sucrose, modified formulations of iron dextran and ferric gluconate. These formulations have much improved safety profiles, lower rates of adverse events and also reduce the frequency of hospital or clinic visits by the patients. Compared with blood transfusions, intravenous (IV) iron therapy is safe and cost effective for restoration of hemoglobin and body iron stores. IV iron sucrose formulations are being used in many countries for the said purpose. Although another IV iron preparation, that is, ferric carboxymaltose is now available and claims to be safe but it is very costly and not affordable by everyone. Our study will help primary physicians to prioritize IV iron sucrose which is safe and easily affordable to treat iron deficiency anemia.

The aim of the study was to compare the efficacy and safety of IV iron therapy with oral iron supplementation in iron deficiency anemia.

Materials and Methods

This is an observational study conducted in the Department of Medicine of SCB Medical College and Hospital, Cuttack, which is a teaching and referral hospital of Eastern India. The study period was from September 2016 to August 2018. Institutional ethical committee approval was obtained prior to the study. Informed written consent was taken from every individual participating in the study in local Odia language.

Inclusion criteria

The study population consisted of persons of age more than 15 years whose hemoglobin level remain between 5 and 10 g/dL and serum ferritin falls below 15 µg/L. A sample size of 100 patients was selected.

Exclusion criteria

Persons with hemoglobin less than 5 g/dL were excluded as they required blood transfusions for immediate improvement in hemoglobin level. Persons with anemia other than iron deficiency and those unwilling to give consent were excluded. Persons with evidence of liver or kidney dysfunction or any form of chronic diseases were also excluded.

Investigations

All participants were subjected to thorough clinical examination, blood investigations such as complete blood count, peripheral blood smear, serum ferritin values, liver and renal function tests, stool examinations for worm infestations and occult blood loss. The patients were divided into two groups consisting of 50 each. One group received calculated dose of IV preparation of iron sucrose (I-maxS injection, each 5 mL contains 100 mg of elemental iron as iron sucrose manufactured by Aristo Pharma Pvt. Ltd, Mumbai, India, and other group received 100 mg of oral ferrous sulfate tablet twice a day for one month. The formula used for calculation of total required IV elemental iron in the form of iron sucrose, that is, total dose infusion (TDI) was: $2.3 \times \text{bodyweight (kg)} \times (15-\text{patient's hemoglobin in g/dL}) +500 \text{mg (for stores)}$. The total calculated TDI was administered within three consecutive days, up to a maximum of 500 mg per day infusion in 500 ml of normal saline over a period of three to four hours. The infusion was given under supervision to avoid any untoward side effects. Any adverse event occurring during or subsequent to the infusions was recorded. After completion of TDI, treatment was deemed to be completed and patients were discharged without oral iron supplementation. All study persons were constantly in touch and were advised for hemoglobin and serum ferritin assessment on day 14 and day 28 of starting of treatment. These time-points were decided based on previous studies.

Statistical analysis

The values were expressed in terms of mean and standard deviation. Student’s t-test was used for comparison of mean hemoglobin levels between the two groups and asymptotic 2-tailed P value of < 0.05 was considered statistically significant. Data were analyzed using SPSS software version 18 (PASW statistics for Windows, Chicago: SPSS Inc).

Results

Total 100 patients were enrolled in the study of which 37 were males and 63 were females. In oral iron group the initial Hb was $6.45 \pm 0.72 \text{ g/dL}$ and in the IV iron group it was $6.34 \pm 0.86 \text{ g/dL}$. On day 14 of the study Hb level raised to $8.84 \pm 0.47 \text{ g/dL}$ in oral iron group and $10.52 \pm 0.61 \text{ g/dL}$ in IV iron group. On day 28 of the study mean Hb level raised to $9.69 \pm 0.47 \text{ g/dL}$ in oral iron group and $11.66 \pm 0.84 \text{ g/dL}$ in IV iron group [Table 1]. On the contrary, the initial serum ferritin level was less than $15 \text{ µg/L}$ in all study patients. On day 14 of oral iron supplementation group and IV iron therapy group, serum ferritin level raised to $33.80 \pm 1.29$ and $148.23 \pm 11.86 \text{ µg/L}$, respectively. On day 28, serum ferritin level dropped to $115.76 \pm 15.30 \text{ µg/L}$ in IV iron therapy group in comparison to $43.61 \pm 8.88 \text{ µg/L}$ in oral iron supplementation group which is highly significant ($P < 0.001$) [Table 2]. The drop in serum ferritin value may be due to rapid use of iron store.

| Hemoglobin (g/dL) | Oral iron (n=50) | IV iron (n=50) | P |
|-------------------|------------------|---------------|---|
| Day 0             | 6.45±0.72        | 6.34±0.86     | 0.601 |
| Day 14            | 8.84±0.47        | 10.52±0.61    | < 0.001 |
| Day 28            | 9.69±0.47        | 11.66±0.84    | < 0.001 |

Table 1: Comparison of hemoglobin levels following oral iron or intravenous iron therapy (N=100)
in IV iron group. Of 100 patients, side effects to therapy were observed in 18 patients of which 12 were in oral iron supplementation group and 6 were in IV iron therapy group [Table 3]. The causes of iron deficiency anemia were found to be gastro-intestinal (GI) bleed in maximum number of cases (43%) in the form of chronic piles and chronic duodenal ulcer followed by menorrhagia (25%). Other causes included hook worm infestation in 4%, chronic malaria in 4%, malabsorption in 10% and nutritional deficiency in 14% of cases. In 4% cases the cause could not be determined.

**Discussion**

The study was done in our hospital to know whether intravenous iron sucrose therapy in iron deficiency anemia is safe and fruitful in the form of raising Hb and iron store in comparison to conventional oral iron supplementation. In our study, of 100 patients 37 were males and 63 were females, which show iron deficiency anemia is more common in females. According to third national family health survey in India, prevalence of iron deficiency anemia among adult males is 24% and in adult females 55% which is also reflected in the study of prevalence of anemia among OPD patients of College of Medicine and J.N.M. Hospital, Kalyani, Nadia by Chattopadhyay et al. In this study, the baseline mean hemoglobin level in the oral iron group was 6.45 ± 0.7263 g/dL and the IV iron therapy group was 6.34 ± 0.8681 g/dL. Fourteen days after starting the therapy there was significant rise in the mean hemoglobin level in both oral and intravenous groups. The mean hemoglobin of oral group raised to 8.84 ± 0.4789 g/dL and intravenous group raised to 10.52 ± 0.6179 g/dL (P < 0.001). After completion of iron therapy on day 28, mean hemoglobin level of oral group was 9.69 ± 0.4712 g/dL and intravenous group was 11.66 ± 0.8437 g/dL which was statistically significant (P < 0.001).

When we compare serum ferritin values in both groups it was found that on day 28 the mean serum ferritin was increased in oral group from 8.30 ± 1.900 µg/L to 43.61 ± 8.8811 µg/L which was statistically significant. (P < 0.001). In IV iron sucrose group serum ferritin level increased from 8.23 ± 4.640 µg/L to 148.23 ± 11.8607 µg/L on day 14 and then found to be decreased to 115.76 ± 15.3070 µg/L. This drop of serum ferritin is due to rapid incorporation of ferritin into bone marrow for erythropoiesis. The sharp and much higher rise of serum ferritin and hemoglobin values in intravenous iron group versus a modest rise in oral group points to the efficacy and rapid response of intravenous iron therapy than oral iron supplementation. Our results are comparable with following studies. Bhandal N. and Russell R. et al. (2006) in their study “intravenous versus oral iron therapy for postpartum anemia” found that there was rapid resolution of hemoglobin and serum ferritin in intravenous iron sucrose group than oral iron therapy. Another study by Giannoulis C. et al. (2009) comprising of 104 study population have found similar results like that of our study. Intravenous iron sucrose is safe, effective and well tolerable in comparison to poor tolerance and prominent gastrointestinal side effects observed with oral ferrous sulfate prescribed for iron deficiency anemia. Similar results were obtained by Bayoumeu F. et al. without serious side effects of intravenous iron sucrose therapy in iron deficiency anemia. Safety of intravenous iron formulations are supported by a meta-analysis consisting of more than 100 randomized controlled trials including the largest PIVOTAL and FINDCKD trials.

Charytan et al. 2005 in their study have found that intravenous iron sucrose is safe and effective in chronic kidney disease (CKD) patients with iron deficiency anemia without serious side effects. Majority of population in developing countries like India fulfil their healthcare needs from primary and community health centers where primary care physicians are major healthcare providers. Pregnant women from rural areas usually present to the antenatal clinics at late gestational age and almost half of them have moderate anemia. Therefore, correction of iron deficiency anemia through oral iron supplements is not possible in a short span of time. Hence, safe and effective parenteral iron formulations can be used as an alternative therapy by primary care physicians in this scenario.

In our study 18 patients developed adverse drug reactions to therapy of which 12 in oral iron supplementation group and 6 in intravenous group. Only one patient developed transient hypotension, one developed fever and four developed arthralgia in intravenous group which were not severe enough to stop intravenous therapy. None of the patients had anaphylaxis. Chandler et al. examined the optimal doses of iron sucrose in their study involving 335 CKD patients and found doses of 200-300 mg intravenously over 2 hr were well tolerated and safe. Patients those received doses of 400-500 mg intravenously within

| Table 2: Comparison of serum ferritin levels following oral iron or intravenous iron therapy (N=100) |
|-----------------|-----------------|-----------------|-----------------|
| Serum ferritin (µg/L) | Oral iron (n=50) | IV iron (n=50) | P      |
| Day 0            | 8.30±1.90       | 8.23±4.64       | 0.282 |
| Day 14           | 33.80±1.29      | 43.61±8.88      | < 0.001|
| Day 28           | 115.76±15.30    | 148.23±11.86    | < 0.001|

| Table 3: Side effects profile of oral iron versus intravenous iron therapy (N=100) |
|-----------------|-----------------|-----------------|
| Side Effects    | Oral iron supplementation (n=50) | Intravenous iron sucrose (n=50) |
| Heart burn      | 2 (4%)          | 0               |
| Nausea          | 2 (4%)          | 0               |
| Vomiting        | 1 (2%)          | 0               |
| Constipation    | 3 (6%)          | 0               |
| Metallic taste  | 3 (6%)          | 0               |
| Diarrhea        | 1 (2%)          | 0               |
| Hypotension     | 0               | 1 (2%)          |
| Anaphylaxis     | 0               | 0               |
| Fever           | 0               | 1 (2%)          |
| Arthralgia      | 0               | 4 (8%)          |
| **Total**       | **12 (24%)**    | **6 (12%)**     |

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Conclusion

In our study, intravenous iron sucrose appeared to be more efficacious in increasing hemoglobin level more rapidly than prolonged course of oral iron therapy. It also replenishes iron stores more rapidly than oral iron. The high dose regimen saves time for both patient and health professionals. Intravenous iron therapy in form of iron sucrose provides complete treatment in most of cases within a short period of time and overcomes the issue of noncompliance. Contrary to the usual belief this modality of treatment has comparatively less side effects and may be recommended for treatment of iron deficiency anemia. We conclude in our study that IV iron sucrose is safe, efficacious and cost effective to treat moderate iron deficiency anemia in a short time. We also recommend further studies with newer IV iron formulations to overcome the issue of affordability and the risks of infusion related complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Farkin F, Chesterman C, Penington D, Rush B. Hypochromic anemia: Iron deficiency and Sideroblastic anemia. De Gruchy’s, Clinical hematology in Medical Practice; Germany: 2008-Blackwell Science Ltd.

2. Benoist De, Cogswell M, Egli I, McLean E. Worldwide Prevalence of Anaemia 1993-2005; WHO Global Database of Anaemia.

3. Gulmezoglu AM, Vilar J, Ngoc NT, Piaggio G, Adetoro L, Abdel-Aleem H, et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001;358:689-95.

4. Cooke M, Lamplugh A, Naudeer S, Edey M, Bhandari S. Efficacy and tolerability of accelerated-dose low-molecular-weight iron dextran (cosmofer) in patients with chronic kidney disease. Am J Nephrol 2012;35:69-74.

5. Agarwal KN, Agarwal DK, Sharma A, Sharma K, Prasad K, Kalita MC, et al. Prevalence of anaemia in pregnant and lactating women in India. Indian J Med Res 2006;124:173-84.

6. Peebles G, Fenwick S. Intravenous iron administration in a short-stay hospital setting. Nurs Stand 2008;22:35-41.

7. Westad S, Backe B, Salvesen KA, Nakling J, Okland I, Borthen I, et al. A 12-week randomised study comparing intravenous iron sucrose versus oral ferrous sulphate for treatment of postpartum anemia. Acta Obstet Gynecol Scand 2008;87:916-23.

8. Adamson JW. Iron deficiency and other hypoproliferative anemias. Harrison’s principles of internal medicine. 2008:628-34.

9. Parewunsnyk G, Huch R, Huch A, Breymann C. Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. Br J Nutr 2002;88:3-10.

10. Rajan SI, James KS. Third national family health survey in India: Issues, problems and prospects. Econ Polit Wkly 2008;43:33-8. JSTOR. Available from: www.jstor.org/stable/40278234. [Last accessed on 2020 Apr 5].

11. Chattopadhyay D, Adhya S. Prevalence of Anaemia among OPD Patients of a Tertiary Care Hospital of Eastern India. IOSR Journal of Dental and Medical Sciences 2013;10:01-3.

12. Beshara S, Lundqvist H, Sundin J, Lubberink M, Tolmachev V, Valind S, et al. Pharmacokinetics and red cell utilization of iron (III) hydroxide-sucrose complex in anaemic patients: A study using positron emission tomography. Br J Haematol 1999;104:296-302.

13. Bhandal N, Russell R. Intravenous versus oral iron therapy for postpartum anemia. BJOG 2006;113:1248-52.

14. Giannoulis C, Danilidis A, Tantanasis T, Dinas K, Tzafettas J. Intravenous administration of iron sucrose for treating anaemia in postpartum women. Hippokratia 2009;13:38-40.

15. Al-Momen AK, Al-Meshari A, Al-Nuaim L, Saddique A, Abotalib Z, Khashogji T, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anaemia during pregnancy. Eur J Obstet Gynecol Reprod Biol 1996;69:121-4.

16. Auerbach M, Gafter-Gvili A, Macdougall IC. Intravenous iron: A framework for changing the management of iron deficiency. Lancet Haematol 2020;7:e342-50.

17. Bayoumeu F, Buisset CS, Baka NE, Legagneur H, Barbarin P, Laxenaire MC. Iron therapy in iron deficiency anemia in pregnancy: Intravenous route versus oral route. Eur J Obstet Gynecol Reprod Biol 2005;123(Suppl 2):s15-s9.

18. Charityan C, Quinbi W, Baille GR. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron Clin Pract 2005;100:55-62.

19. Jacob OM, Kant S, Haldar P, Kaur R, Dadhwal V, Prakash S. Intravenous Iron sucrose and change in hemoglobin, ferritin, and oxidative stress markers among moderately anemic pregnant women attending a secondary care level Hospital in Northern India. Indian J Public Health 2020;64:11-6.

20. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: Establishing a safe dose. Am J Kidney Dis 2001;38:988-91.