ORIGINAL ARTICLE

Role of Iron Isomaltoside 1000 in Treatment of Iron Deficiency Anemia in Obstetrics and Gynecological Patients

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Abstract

Background: Pregnant women are particularly susceptible to iron deficiency anemia (IDA), a global health problem. Having an IDA is associated with poor outcomes for both the mother and the child. Due to the variety of laboratory tests available, the most commonly used are hemoglobin (Hb) and serum ferritin (SF). The standard treatment for IDA is intravenous (IV) iron.

Aim and objective: Iron isomaltoside (IIM) 1000 (Rapifer IV) treatment in pregnant and gynecological patients was evaluated in this study.

Materials and methods: Fifty pregnant women who were followed from the start of the second trimester until a few days before delivery were studied for IDA. For a minimum of 15 minutes, all women received the same dose of IIM 1000 mg (Rapifer IV). To determine the efficacy of the treatment plan, several tests were conducted, including estimations of Hb, red blood cell (RBC) count, white blood cell (WBC) count, platelet count, polymorphs, lymphocytes, eosinophils, monocytes, packed-cell volume (PCV), and mean corpuscular volume (MCV). When the ferritin level is 30 gm/L, severe iron deficiency (ID) is defined, while a mild-moderate ID is determined when the ferritin level is between 100 and 30 gm/L.

Results: Mean age of women with IDA was 35.14 ± 7.183 which ranged from 22 to 53 years. Significant improvement in mean Hb (8.64 ± 0.85 vs 12.86 ± 0.97, p <0.001), platelet count (115.11 ± 161.22 vs 3.13 ± 0.68, p < 0.001), polymorphs (70.9 ± 34.36 vs 50.62 ± 6.39, p = 0.0001), lymphocytes (32.24 ± 9.70 vs 39.68 ± 7.64, p = 0.0001), PCV (31.40 ± 4.46 vs 39.72 ± 2.56, p = 0.023), MCV (74.51 ± 8.23 vs 87.14 ± 3.05, p = 0.021), mean corpuscular hemoglobin (MCH) (23.71 ± 3.77 vs 31.62 ± 2.10, p = 0.012), mean corpuscular hemoglobin concentration (MCHC) (27.56 ± 2.81 vs 34.90 ± 2.30, p = 0.001), red cell distribution width (RDW) (18.48 ± 3.02 vs 13.94 ± 1.62, p = 0.004), total iron binding capacity (TIBS) (397.1 ± 74.53 vs 273.86 ± 31.55, p = 0.024), SF (32.19 ± 78.18 vs 85.96 ± 21.74, p <0.001), serum iron (46.40 ± 14.89 vs 108.32 ± 21.38, p <0.001), and reticulocytes (1.84 ± 0.79 vs 1.07 ± 0.29, p <0.001) after 27th day treatment with IIM 1000 compared to baseline. A significant improvement in Hb was observed in obstetrics and gynecological (12.68 from 8.24; p <0.001) and postoperative women (13.22 from 8.62; p <0.001). IIM 1000 was also able to improve severe ferritin level to mild-moderate ferritin level in a span of 27 days.

Conclusion: IIM 1000 (Rapifer IV) is efficacious in obstetrics and gynecological and postoperative women. A significant improvement was observed on the classical parameters of IDA.

Keywords: Iron deficiency anemia, Iron isomaltoside 1000, Serum ferritin, hemoglobin.

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Introduction

Postpartum IDA is associated with low birth weight and preterm delivery and maternal and neonatal mortality rates, lactation problems, postpartum depression, and early-childhood IDA.[1] When severe IDA is present, oral iron supplementation reduces the risk of maternal ID or anemia by 57–70%.[2] Maternal IDA and nonanemic ID with severe symptoms after the first trimester are safe and effective with IV iron treatment.[3]

Within 24 hours of infusion, all IV formulations can cause self-limiting allergic reactions, resolve without treatment, and rarely return with reinfusion.[4] Most of the responses to IV iron formulations are caused by CARPA reactions to infusion nanoparticles.[5] The most common symptoms of these self-limiting acute hypersensitivity reactions are flushing and an immediate tightness in the chest or back but no hypotension, wheezing, stridor, or periorbital edema. Life-threatening hypersensitivity reactions to IV iron preparations are infrequent.[6] This risk is estimated to be 0.06% for IV (IIM, Rapifer 500).[7]

Iron isomaltoside was studied in various clinical settings to see if it affected a variety of clinical parameters.[8] However, only a few studies have compared the relative effects of IIM in obstetrics and gynecological patients to date. IIM 1000 was studied to see if it was safe and effective for treating anemia in pregnant women with ID in this study.

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Materials and Methods

In the present prospective interventional study, 50 patients with IDA were evaluated for efficacy and safety at the Institute Of Kidney Diseases And Research Centre in Ahmedabad from March 2020 to March 2021.

After obtaining informed consent from institutional review board (IRB), written informed consent was obtained from all the patients.

Pregnant women from the beginning of the second trimester until a few days before delivery who received IIM 1000 (Rapifer IV) at the Maternity Ward were included. Women who had prior IIM 1000 infusion and did not give written informed consent were excluded.

Women who weighed less than 75 kg at their initial visit to the maternity care unit (usually, gestational week 10–12) received 1000 mg IIM (Rapifer IV) over a minimum of 15 minutes. Three trained nurses delivered the infusions at the study's specialized antenatal care center.

The pregnant woman was instructed to lie on her back in a comfortable bed in a quiet room. There is a possibility of a mild but quickly reversible reaction. She was also told that the nurses would be well-versed in dealing with the response and would assist her in any way necessary. The nurse was in the patient's room for the first few minutes of the infusion, and they remained in constant communication after that.

The occurrence of adverse drug reactions (ADRs) was noted as a safety factor. Platelets ($\times10^3$/mm^3), total WBCs ($\times10^3$/mm^3), hemoglobin ($\times10^3$/mm^3), eosinophils ($\times10^3$/mm^3), and polymorphs ($\times10^3$/mm^3) are all important indicators of treatment success. Other factors to consider include the percentage of polymorphs, lymphocytes, eosinophils, and monocytes in the blood, as well as the percentage of packed cells in the blood, the percentage of end of study.

An ID can be classified as severe or mild-moderate depending on the ferritin level, with a ferritin level of 30 gm/L or greater indicating severe ID.

Data analysis was carried out using IBM Statistical Package for the Social Sciences (SPSS) version software for the social sciences. The study cohort's baseline characteristics were determined by conducting a descriptive analysis. Mean and standard deviation describe quantitative variables, whereas numbers and percentages describe categorical variables. There were two means, so a paired *t*-test was used to determine significance. The correlation between percentages and numbers was done using the Chi-square test. A *p*-value of less than 0.05 is considered significant.

Results

The mean age of the study cohort was 35.14 ± 7.183 years which ranged from 22 to 53 years. IDA was more prevalent in the age group of 31–40 years [27 (54%)] followed by 21–30 [12 (24%)] and 41–50 [10 (20%)] (Tables 1 to 7). A significant improvement was observed in ferritin level assessed by severity level. All the patients with severe ferritin levels (86%) had turned to mild-moderate ferritin levels (p <0.001) (Fig. 1).

Table 1: Descriptive analysis for baseline characteristics

Parameters	*Baseline*
Age (years)	35.14 ± 7.183
Hb (gm%)	8.64 ± 0.85
RBC ($\times10^6$/mm^3)	4.22 ± 6.23
Total WBC ($\times10^3$/mm^3)	12.56 ± 4.13
Platelet count ($\times10^3$/mm^3)	115.11 ± 161.22
Polymorphs (%)	70.9 ± 34.36
Lymphocytes (%)	32.24 ± 9.70
Eosinophils (%)	1.34 ± 0.99
Monocytes (%)	1.2 ± 0.87
PCV (%)	31.40 ± 4.46
MCV (fL)	74.51 ± 8.23
MCH (pg)	23.71 ± 3.77
MCHC	27.56 ± 2.81
RDW	18.48 ± 3.02
S. TIBC	397.1 ± 74.53
S. Ferritin	32.19 ± 78.18
S. Iron	46.40 ± 14.89
Reticulocytes (%)	1.84 ± 0.79

Data are expressed as mean ± standard deviation. Hb, hemoglobin; RBCs, red blood cells; WBC, white blood cells; PCV, packed-cell volume; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; TIBC, total iron-binding capacity

Discussion

IV iron formulations may aid patients with a moderate or severe ID or a deficiency that is resistant to oral iron therapy. Parenteral iron was formerly used with extreme caution and as a last choice due to a poor safety profile, particularly anaphylactic responses. Iron dextran parenteral therapy was associated with 31 deaths between 1976 and 1996. Acute adverse effects of IV iron are unpredictable and vary according to the iron preparation used and the recipient's preexisting morbidity.[9] This study aimed to determine the efficacy of IIM 1000 mg (Rapifer IV) in treating IDA in obstetrics and gynecological patients.

Laboratory testing is a critical component of diagnosing IDA. A reduction in Hb, serum iron concentration, serum transferrin saturation, SF level, and TIBC are all common laboratory findings in IDA. A complete blood count and SF level are sufficient for diagnosis. A SF content of 30 gm/L paired with a Hb concentration of 11 gm/dL during the first trimester, 10.5 gm/dL during the second trimester, and 11 gm/dL during the third trimester is used to identify anemia during pregnancy.[10] SF concentration is the most accurate test in patients without underlying inflammation, and a SF level less than the threshold value is sufficient for diagnosis in the absence of other tests; however, physicians should be aware that SF is also an acute-phase reactant and may be typical, even elevated, in inflammatory conditions despite the presence of other symptoms.[11] The present study found significant improvement in mean Hb, platelet count, polymorphs, lymphocytes, PCV, MCV, MCH, MCHC, and RDW. A significant improvement was observed in ferritin level assessed by severity level. All the patients with severe ferritin levels (86%) had turned to mild-moderate ferritin levels (p <0.001).

Additional tests, such as transferrin saturation, serum iron, TIBC, and C-reactive protein (CRP), are needed to diagnose anemia when Hb levels are low (11 gm/dL in the first trimester, 10.5 in the second trimester, and 11 gm/dL in the third trimester) but SF is normal (30 gm/L). The diagnosis of thalassemia may be made if the SF level is normal (30 gm/L), but the MCV is low (70 fL).[10,12] In the present study, serum TIBS, serum iron, and reticulocytes were also significantly improved after IIM 1000 (Rapifer IV).

Only 20% of the 50 women who received IV-IIM in this study experienced mild ADRs at the end of Day 27. According to our findings, a single high-dose IV-IIM infusion (up to 1000 mg) during pregnancy is safe for treating IDA in this population. As previously reported,[13] we found no correlation between the iron dose and the frequency of ADRs. According to a 2018 meta-analysis, three

Table 2: Comparing the changes observed after 27 days after the administration of IIM 1000 (Rapifer IV)

Parameters	*Baseline*	*After 27 days*	*p-value*
Hb (gm%)	8.64 ± 0.85	12.86 ± 0.97	<0.001
RBC ($\times 10^6/mm^3$)	4.22 ± 6.23	3.59 ± 0.59	0.484
Total WBC ($\times 10^3/mm^3$)	12.56 ± 4.13	12.26 ± 1.10	0.645
Platelet count ($\times 10^3/mm^3$)	115.11 ± 161.22	3.13 ± 0.68	<0.001
Polymorphs (%)	70.9 ± 34.36	50.62 ± 6.39	0.0001
Lymphocytes (%)	32.24 ± 9.70	39.68 ± 7.64	0.0001
Eosinophils (%)	1.34 ± 0.99	1.16 ± 0.75	0.303
Monocytes (%)	1.2 ± 0.87	1 ± 0.84	0.242
PCV (%)	31.40 ± 4.46	39.72 ± 2.56	0.023
MCV (fL)	74.51 ± 8.23	87.14 ± 3.05	0.021
MCH (pg)	23.71 ± 3.77	31.62 ± 2.10	0.012
MCHC	27.56 ± 2.81	34.90 ± 2.30	0.001
RDW	18.48 ± 3.02	13.94 ± 1.62	0.004
S. TIBC	397.1 ± 74.53	273.86 ± 31.55	0.024
S. Ferritin	32.19 ± 78.18	85.96 ± 21.74	<0.001
S. Iron	46.40 ± 14.89	108.32 ± 21.38	<0.001
Reticulocytes (%)	1.84 ± 0.79	1.07 ± 0.29	0.002

Data are expressed as mean ± standard deviation. Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PCV, packed-cell volume; RBCs, red blood cells; RDW, red cell distribution width; TIBC, total iron-binding capacity; WBC, white blood cells

Table 3: Comparing peripheral smear findings

Peripheral smear findings	*Baseline*	*After 27 days*	*p-value*
Dimorphic blood picture with neutrophilia	1 (2)	0 (0)	<0.001
Microcytic hypochromic blood picture	22 (44)	0 (0)	
Microcytic hypochromic, anisocytosis	22 (44)	1 (2)	
Normocytic hypochromic	1 (2)	0 (0)	
Normocytic normochromic	4 (8)	49 (98)	
Grand total	50 (100)	50 (100)	

Table 4: Effect of IIM 1000 (Rapifer IV) on severity index based on ferritin level

Serum ferritin level	*Baseline*	*After 27 days*	*p-value*
Mild-moderate	4 (8)	42 (84)	<0.001
Severe	43 (86)	0 (0)	
Adequate	3 (6)	8 (16)	

Data are expressed as the number of patients (percentage)

Table 5: Comparing improvement in mean Hb in different age groups

Age group	*Baseline*	*After 27 days*	*p value*
21–30	8.58	13.03	<0.001
31–40	8.68	12.68	<0.001
41–50	8.62	13.17	<0.001

Table 6: Comparing improvement in mean ferritin in different age groups

Age group	*Baseline*	*After 27 days*	*p-value*
21–30	158.93	1033.19	0.001
31–40	844.32	2475.46	0.001
41–50	574.14	798.60	0.021

Out of 50 patients who received IIM 1000 (Rapifer IV), only 10 (20%) had reported any adverse effects

Table 7: Comparing improvement in hemoglobin in obstetrics and gynecological and postoperative women

Age group	*Type*	*Baseline*	*After 27 days*	*p-value*
<35 years	Obstetrics and gynecology ($n = 28$)	8.24	12.68	<0.001
21–50	Postoperative	8.62	13.22	<0.001

different IV iron therapies (not IIM) had a median prevalence of treatment-related mild ADRs in pregnancy ranging from 2.2 to 6.7%.[14] One hundred twenty-one women in the study who received IV-IIM experienced four cases of mild, easily reversible ADRs, according to a 2017 poster from England. According to that study, individuals who received less than or more than 1000 mg of iron experienced the same number of ADRs.[15]

In the present study, we also observed a significant improvement in Hb in obstetrics and gynecological and postoperative women.

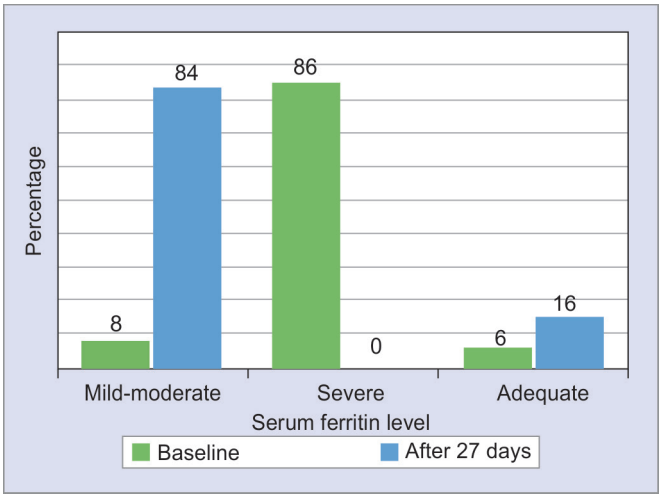

Fig. 1: Effect of IIM 1000 (Rapifer IV) on severity index based on ferritin level

This highlights the importance of IIM 1000 (Rapifer IV) in improving Hb in all sets of women.

Iron isomaltoside (IIM) 1000 (Rapifer IV) contains an iron moiety and a carbohydrate moiety, with the iron tightly bonded to the carbohydrate in the form of a matrix. This reduces the risk of toxicity from labile iron release by allowing a controlled and delayed release of iron to iron-binding proteins. There are 3–5 glucose units in each isomaltoside 1000 chain, giving it a molecular weight of 1000 Da.[13] Iron dextran contains branching dextran polysaccharides, in contrast to isomaltoside 1000 (Rapifer IV), which is linear and unbranched.[16] It is possible to administer high doses of IIM (single doses of 1–2 g) in a short period because of the tightly bonded iron. Compared to molecules with more loosely bound iron, the IIM complex appears to be less oxidatively stressful and immunologically toxic.[16–18]

Conclusion

People worldwide, especially pregnant women, are at risk from IDA, a significant disease. IV IIM 1000 (Rapifer IV) therapy is an alternative treatment option for patients with moderate or severe ID. We observed significant improvement in mean Hb, platelet count, polymorphs, lymphocytes, PCV, MCV, MCH, MCHC, RDW, TIBS, serum iron, and reticulocytes after treatment with IIM 1000. Obstetrics and gynecological and postoperative women also showed a significant improvement. IIM 1000 also improved severe ferritin level to mild-moderate ferritin level in 27 days.

References

1. Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematol Am Soc Hematol Educ Program 2016;2016(1):57–66. DOI: 10.1182/asheducation-2016.1.57.
2. Tolkien Z, Stecher L, Mander AP, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One 2015;10(2):e0117383. DOI: 10.1371/journal.pone.0117383.
3. Wesström J. Safety of intravenous iron isomaltoside for iron deficiency and iron-deficiency anemia in pregnancy. Arch Gynecol Obstet 2020;301(5):1127–1131. DOI: 10.1007/s00404-020-05509-2.
4. Bircher AJ, Auerbach M. Hypersensitivity from intravenous iron products. Immunol Allergy Clin North Am 2014;34(3):707–723. DOI: 10.1016/j.iac.2014.04.013.
5. Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms, and management. Br J Pharmacol 2015;172(21):5025–5036. DOI: 10.1111/bph.13268.
6. Kalra PA, Bhandari S. Efficacy and safety of iron isomaltoside (Monofer®) in the management of patients with iron deficiency anemia. Int J Nephrol Renovasc Dis 2016;9:53–64. DOI: 10.2147/IJNRD.S89704.
7. Kalra PA, Bhandari S. Safety of intravenous iron use in chronic kidney disease. Curr Opin Nephrol Hypertens 2016;25(6):529–535. DOI: 10.1097/MNH.0000000000000263.
8. Bhandari S, Kalra PA, Berkowitz M, et al. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: The FERWON-NEPHRO randomized, open-label, comparative trial. Nephrol Dial Transplant 2021;36(1):111–120. DOI: 10.1093/ndt/gfaa011.
9. Chandra I, Sun L. Iron status and choice of iron therapy during pregnancy: advantages and disadvantages. Int J Reprod Contracept Obstet Gynecol 2015;4:1264–1271. DOI: 10.18203/2320-1770.ijrcog20150695.
10. Api O, Breyman C, Çetiner M, et al. Diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period: Iron deficiency anemia working group consensus report. Turk J Obstet Gynecol 2015;12(3):173–181. DOI: 10.4274/tjod.01700.
11. Breymann C, Honegger C, Holzgreve W, et al. Diagnosis and treatment of iron-deficiency anaemia during pregnancy and postpartum. Arch Gynecol Obstet 2010;282(5):577–580. DOI: 10.1007/s00404-010-1532-z.
12. Pavord S, Myers B, Robinson S, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2012;156(5):588–600. DOI: 10.1111/j.1365-2141.2011.09012.x.
13. Kalra PA, Bhandari S, Saxena S, et al. A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis-dependent chronic kidney disease patients with anaemia. Nephrol Dial Transplant 2016;31(4):646–655. DOI: 10.1093/ndt/gfv293.
14. Qassim A, Mol BW, Grivell RM, et al. Safety and efficacy of intravenous iron polymaltose, iron sucrose and ferric carboxymaltose in pregnancy: a systematic review. Aust N Z J Obstet Gynaecol 2018;58(1):22–39. DOI: 10.1111/ajo.12695.
15. Minogue A, Branstorm M, Westromm A, et al. Poster: consultant haematologist review of intravenous iron service in pregnant women at Queen's Hospital, Romford. Romford, UK: Transfusion Practitioner and Consultant Haematologist, Queen's Hospital; 2017.
16. Jahn MR, Andreasen HB, Futterer S, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications. Eur J Pharm Biopharm 2011;78(3):480–491. DOI: 10.1016/j.ejpb.2011.03.016.
17. Fell LH, Zawada AM, Rogacev KS, et al. Distinct immunologic effects of different intravenous iron preparations on monocytes. Nephrol Dial Transplant 2014;29(4):809–822. DOI: 10.1093/ndt/gft524.
18. Fell LH, Zawada AM, Seiler S, et al. Impact of individual IV iron preparations on differentiation of macrophages and dendritic cells [poster FO014]: poster presented at 52nd Congress of ERA-EDTA; May 28–31, 2015; London, UK.