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Original Research Article

To observe the rise in haemoglobin concentration levels by parenteral iron infusion of iron isomaltoside 1000 (Fur-IV) in gynaecological patients suffering from iron deficiency anaemia

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ABSTRACT

Introduction: Iron Isomaltoside 1000 (Fur-IV) is a combination of iron and isomaltoside 1000(carbohydrate) which are strongly bound allowing slow and controlled release thereby reducing risk of free iron toxicity and offers high dose flexibility and administration and convenience. It is shown to be effective in treating iron deficiency anaemia across multiple therapeutic groups and compared to IV iron sucrose, Ferric carboxymaltose, and oral iron. It is effective and well tolerated in treatment of anaemia across different therapeutic areas with favourable safety profile.
Aims & Objective: To observe the rise in level of haemoglobin concentration in gynaecological patients suffering from iron deficiency anaemia via single infusion of iron isomaltoside 1000 (Fur-IV).
Study Design: A prospective, observational study.
Materials and Methods: Total 50 women who were attending OPD or an indoor patient of obstetrics and gynaecology department who were diagnosed with iron deficiency anaemia and confirming to inclusion criteria were enrolled and observed in this study. Written and informed consent were taken from all patients and data were recorded in the case record form. Detailed medical history and iron demand of the patient were taken and calculated before administration of IV Iron Isomaltoside 1000 by our department of OBGY. Data of the patients who were enrolled in the study were recorded including their haemogram report before administration and repeat haemogram at 1^{st} and 2^{nd} week after administration. We did the study from May, 2021 to June, 2022 in OBGY department of Scientific Research Institute, Surendranagar, Gujarat, India.
Results: There were no serious adverse events (AE) reported. Only 6 patients reported adverse events [mild nausea, vomiting n=2; fetal bradycardia, n=2; pruritus, n=1; giddiness, n=1. Mean change in Hb is evaluated in 50 patients, increased significantly from 8.63 ± 1.18 gm/dl at baseline to 10.74 ± 1.08 gm/dl (difference of 2.11 ± 0.77 gm/dl; $p < 0.001$) at 2 weeks post-treatment. Safety and efficacy of Fur-IV was rated by physicians as 'excellent and good' in 98% patients.
Conclusion: Iron isomaltoside 1000 (Fur-IV) has demonstrated robust efficacy in patients suffering from Iron deficiency anaemia due to pregnancy. The wide dosing range of Iron isomaltoside allows iron correction in a single visit with minimal risk of anaphylaxis and is thus cost-effective for health-care system.

1. Background

Iron deficiency is common during the pregnancy. If this deficiency left untreated, it can lead to iron deficiency

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anaemia. Prevalence of the iron deficiency anaemia increases through the trimesters which show that women with the iron deficiency in the beginning of pregnancy have a great risk of developing iron deficiency anaemia during pregnancy. The treatment of iron deficiency anaemia depends on cause and severity, time remaining until delivery, severity of anaemia, additional risks, maternal comorbidity and patients' wishes. Most widely used therapeutic approaches include oral and parenteral routes. Oral iron therapy can be switched to parenteral therapy in conditions such as weak or absent response to oral iron, low absorption due to intestinal disease, intolerance of oral iron, the need for rapid and adequate treatment or lack of compliance.[1] In our study we have used one of the IV parenteral iron preparation [Iron Isomaltoside 1000] in gynaecological patients suffering from iron deficiency anaemia.

2. Introduction

Iron is the most abundant element and essential trace mineral necessary for the metabolic reactions in the body which include the role in catalytic enzymes and proteins for DNA synthesis, transport of the oxygen in haemoglobin and myoglobin, oxidative phosphorylation and adenosine triphosphate (ATP) formation in the tricarboxylic acid cycle, mitochondrial cell respiration.[2–4]

Iron deficiency anaemia is common during pregnancy. Global estimates have shown the prevalence of the anaemia in the pregnancy which is 41.8% and as per the data 29% (496 million) of non-pregnant women and 38% (32.4 million) of pregnant women aged 15-49 years were anaemic; among those women about 20 million had severe anaemia.[5] In nearly 50% of the cases, iron deficiency was the etiologic cause while occult iron deficiency in the absence of anaemia was estimated to be between 30-60% in pregnant women.[6] Generally, anaemia is associated with certain factors like reduced quality of life, progression of the disease and poorer outcomes,[2,4] so it is of high priority to treat the anaemia. Parenteral (IV) iron offers a rapid and efficient means of iron correction, and it is superior to the oral iron therapy in many circumstances.[7] Parenteral iron therapy is widely used for treatment of iron deficiency in various disease groups. Parenteral iron preparations are the compounds which contain iron in the core surrounded by carbohydrate shell. Currently marketed intravenous iron agents are: iron sucrose, Ferric carboxymaltose, and iron isomaltoside 1000 (Fur-IV).

Iron isomaltoside 1000 (Fur-IV) is an oligosaccharide with a molecular weight of 1,000 Da, and consists of linear and unbranched chains of 3-5 glucose units.[8] It is a combination of iron and isomaltoside 1000 (carbohydrate) which are strongly bound allowing the strong and controlled release thereby reducing risk of free iron toxicity which offers the high dose flexibility (single dose of 1-2 gm) over a shorter period of time and administration and convenience. Iron isomaltoside complex potentially leads to generation of lesser immunological toxicity and lesser oxidative stress, compared to other compounds with loosely bound iron complex.[9,10]

Iron isomaltoside 1000 is rapidly taken up by the cells in reticuloendothelial system (RES) particularly in the liver and spleen following IV administration, from where iron is slowly released. The plasma half-life is 5 hr for unbound circulating iron and for total iron (bound and circulating) plasma half-life is 20 hr. Circulating iron is removed from the plasma by cells of the RES, which split iron isomaltoside complex into its components of iron and isomaltoside 1000. The iron is immediately bound to the protein moieties which is easily available to form haemosiderin or ferritin, which is physiological storage forms of iron, or to a lesser extent, to transferrin- the transport molecule. This form of iron is subjected to physiological control, replenishes haemoglobin and depleted iron stores. Intact iron isomaltoside is not eliminated via the kidneys due to the size of the carbohydrate-iron complex. The small quantities of iron are eliminated in faeces and urine. The carbohydrate component of iron isomaltoside 1000 is either metabolized or excreted.

Iron deficiency anaemia occurring in the 1^{st} trimester of pregnancy can be treated with oral iron in many cases. Treatment with Fur-IV should be confined to second and third trimester if benefit is judged to outweigh the potential risk for both the mother and the fetus. Fetal bradycardia may occur following parenteral administration. Usually, it is transient and a consequence of a hypersensitivity reaction in mother. Fetus should be carefully monitored during IV administration of parenteral iron to pregnant women. A clinical study showed that the transfer of iron from Fur-IV to human milk is very low, therefore therapeutic dose of Fur-IV anticipated in lactating women, as there is no effect on breastfed newborns/infants.[11]

The clinical efficacy and safety data is available for patients who were given iron isomaltoside with iron deficiency anaemia requiring iron therapy,[12–20] non-anaemic patients undergoing cardiac surgery,[21] and women with post-partum haemorrhage [PPH].[22,23]

3. Materials and Methods

3.1. Study design

A prospective, randomized, observational, single centre study conducted in Scientific Research Institute, Surendranagar, Gujarat, India from May 2021 to June 2022 in 50 women who were attending OPD or an indoor patient of obstetrics and gynaecology department who were diagnosed with iron deficiency anaemia and confirming to inclusion criteria were enrolled and observed in this study. Written and informed consent were taken from all patients

and data were recorded in the case record form.

Detailed medical history and iron demand of the patient (via Ganzoni formula- 2.4 x Hb deficit in gm% (12-patients's Hb) x body weight) were taken and calculated before administration of IV Iron Isomaltoside 1000 by our department of OBGY. The data of patient who were enrolled were recorded including their pathological reports before administration and repeat haemogram at 1^{st} and 2^{nd} week after administration.

3.2. Ethical aspect

The study will begin after the approval of study protocol by Institutional Review Board and written permission from Department of Obstetrics and Gynaecology. Confidentiality of all the data will be maintained. The study will be used for academic and publication purpose only.

3.3. Inclusion criteria

All female patients greater than or equal to age of 18 years attending OPD or indoor suffering from iron deficiency anaemia in whom oral iron preparation are ineffective or clinical need to deliver iron rapidly.

Patients who are willing to give informed consent for the study and are agreeing to follow up.

3.4. Exclusion criteria

1. Female age <18 years
2. Patients who are not willing to give informed consent
3. Presence of severe anaemia Hb < 6 mg/dl
4. Patients known to be allergic to IV iron compounds
5. H/O Chronic liver diseases
6. Patient is known case of thalassemia
7. Signs and symptoms of cardiac failure
8. Increased creatinine >2mg/dl

4. Results

Demographics and baseline characteristics are summarized in Table 1.

Table 1: Basic demographic profile of study participants

Total number of patients	50
Age (years; mean ± S.D.)	27.84 ± 5.30
Weight (kg; mean ± S.D.)	61.67 ± 11.41
Mild anaemia (10-10.9 gm/dl)	6 (12%)
Moderate anaemia (7.1-9.9 gm/dl)	43 (86%)
Severe anaemia (<7 gm/dl)	1 (2%)
Baseline haemoglobin (Hb) (gm/dl; mean ± S.D.)	8.63 ± 1.18

Total 50 adult female patients with mean age of 27.84 ± 5.30 years, mean weight of 61.67 ± 11.41 kg and mean baseline Hb of 8.63 ± 1.18 gm/dl were treated with Fur-IV as shown in Table 1. Most of the patients (86%) were having moderate anaemia.

Table 2: Medical history and physical examination of study participants

Co-morbid conditions	
Diabetes mellitus	1 (2%)
Hypertension	14 (28%)
Hypothyroidism	3 (6%)
Normotensive	36 (72%)
History of anaemia related complications	
Weakness	25 (50%)
Leg cramps	7 (14%)
Vertigo	2 (4%)
Tachycardia	9 (18%)
Asymptomatic	16 (32%)

Among 50 patients, 18 patients (36%) were having co-morbid conditions (diabetes mellitus, hypertension, and hypothyroidism) and were receiving disease-specific treatment and 72% women are Normotensive.

History of anaemia related complications are present in 34 (68%) women and 16 (32%) are asymptomatic. Only 9 (18%) women had tachycardia (increased heart rate >100 bpm) which was returned to normal after advising them to rest for a while.

4.1. Iron isomaltoside dosing

Fur-IV was administered as slow IV infusion by diluting 1000 mg of iron isomaltoside (2 ampoules of 5 ml) in 500 ml of 0.9% normal saline. Duration of treatment is about 45 min.

Table 3: Assessment of efficacy

Parameters	**Haemoglobin (Hb) (gm/dl; mean ± S.D.)**
Baseline	8.63 ± 1.18
1 week	9.47 ± 1.10
2 weeks	10.74 ± 1.08

Table 3 shows assessment of efficacy of Fur-IV. Mean change in Hb is evaluated in 50 patients, increased significantly from 8.63 ± 1.18 gm/dl at baseline to 10.74 ± 1.08 gm/dl (difference of 2.11 ± 0.77 gm/dl; $p < 0.001$) at 2 weeks post-treatment (Figure 1).

Table 4: Safety assessment

Adverse events (Mild)	**n**
Nausea, Vomiting	2
Fetal bradycardia	2
Pruritus	1
Giddiness	1

Table 4 shows safety assessment after giving Fur-IV by noticing adverse events in patients within 2 hours. Fur-IV

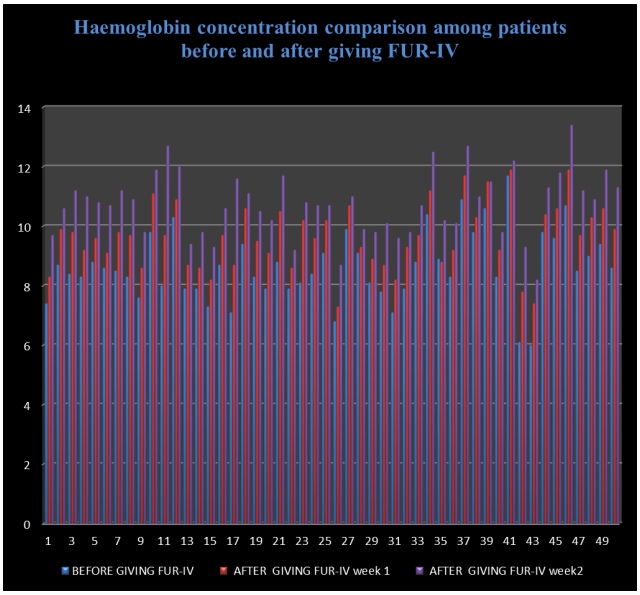

Fig. 1: Comparison of haemoglobin concentration among patients before and after giving Fur-IV treatment]

was well tolerated in majority of patients. Only 6 patients reported adverse events [mild nausea, vomiting n=2; fetal bradycardia, n=2; pruritus, n=1; giddiness, n=1. There were no serious adverse events reported and no any casualties reported.

Table 5: Overall global assessment

Assessment	**n (%)**
Of efficacy	
Excellent	34 (68%)
Good	15 (30%)
Fair	01 (02%)
Poor	00 (00%)
Assessment of Tolerability	
Excellent	42 (84%)
Good	07 (14%)
Fair	01 (02%)
Poor	00 (00%)

Table 5 shows overall global assessment of efficacy and tolerability of iron isomaltoside (Fur-IV). Safety and efficacy of Fur-IV was rated by physicians as 'excellent and good' in 98% patients.

5. Discussion

We analysed 50 patients with iron deficiency anaemia and give them single infusion of 1000 mg iron isomaltoside diluted in 500 ml of 0.9% of normal saline over about 45 minutes and efficacy of haematological parameter (Hb) assessed with its safety and tolerability. In general, greater improvement in haematological parameter (Hb) was observed after IV iron isomaltoside treatment. Mean change in Hb is evaluated in 50 patients, increased significantly from 8.63 ± 1.18 gm/dl at baseline to 10.74 ± 1.08 gm/dl (difference of 2.11 ± 0.77 gm/dl; $p < 0.001$) at 2 weeks post-treatment. Iron isomaltoside administration was well tolerated and there was no any serious adverse drug reaction observed. Some women with iron deficiency anaemia may suffer from various symptoms including fatigue, leg cramps, vertigo, reduced quality of life, headache and dizziness. Thus, it is highly important to treat women with anaemia and the iron isomaltoside drug profile seems optimal as these women need fast correction of their iron deficit, and they are unlikely to attend the hospital for multiple IV iron infusions of lower IV iron dose.

6. Conclusion

New IV iron preparations are capable of delivering a wide dosing range to allow iron correction in a single or low number of visits, a rapid infusion, and minimal potential side effects including labile iron release, and minimal risk of anaphylactic reactions. Furthermore, they are convenient for the patient and the health-care professional, and cost effective for the health-care system. The intention behind the development of iron isomaltoside 1000 (Fur-IV) was to fulfil these requirements. It has a low immunogenic potential, a low potential to generate non transferrin bound iron (NTBI), and does not appear to be associated with clinically significant hypophosphatemia. This trial contributes to the body of evidence demonstrating that Iron isomaltoside is safe and efficacious in treatment of Iron deficiency anaemia in a single visit.

In conclusion, in our study, single infusion of iron isomaltoside 1000 (Fur-IV) has demonstrated robust efficacy and a good safety profile in gynaecological patients suffering from iron deficiency anaemia.

7. Source of Funding

None.

8. Conflict of Interest

None.

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