Original Article

Oral high-dose sucrosomal iron vs intravenous iron in sideropenic anemia patients intolerant/refractory to iron sulfate: a multicentric randomized study

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Abstract
Iron deficiency anemia is among the most frequent causes of disability. Intravenous iron is the quickest way to correct iron deficiency, bypassing the bottleneck of iron intestinal absorption, the only true mechanism of iron balance regulation in human body. Intravenous iron administration is suggested in patients who are refractory/intolerant to oral iron sulfate. However, the intravenous way of iron administration requires several precautions; as the in-hospital administration requires a resuscitation service, as imposed in Europe by the European Medicine Agency, it is very expensive and negatively affects patient’s perceived quality of life. A new oral iron formulation, Sucreosomal iron, bypassing the normal way of absorption, seems to be cost-effective in correcting iron deficiency anemia at doses higher than those usually effective with other oral iron formulations. In this multicentric randomized study, we analyze the cost-effectiveness of intravenous sodium ferrigluconate vs oral Sucreosomal iron in patients with iron deficiency anemia refractory/intolerant to oral iron sulfate without other interfering factors on iron absorption.

Keywords Iron deficiency anemia · Intravenous sodium ferrigluconate · Oral Sucreosomal iron · High doses · Refractoriness/intolerance to oral iron sulfate

Introduction

Iron deficiency anemia (IDA) is among the five most frequent causes of disability in humans [1]. Anemia affects one-third of the world population and IDA is the first cause, regarding 1.24 billion of individuals [1, 2]. WHO estimates that 50% of anemia cases worldwide are due to IDA [3] and prevalence of iron deficiency anemia in Europe was estimated about 20% [4, 5].

Iron deficiency (ID) manifests in two forms: absolute or functional. The first one is due to a total body iron stores lack. The second one is present in diseases in which total body iron stores are normal or increased, but iron supply to the bone marrow is inadequate because of reduced iron bioavailability, as in many acute and chronic inflammatory diseases. Absolute and functional iron deficiencies can co-exist [6].

Sucrosomial® iron (SI) is a new oral iron formulation, in which ferric pyrophosphate is protected by a phospholipid bilayer membrane composed mainly by sunflower lecithin, enveloped in a sucrester matrix stabilized by other ingredients as tricalcium phosphate and starch, forming the “sucrosome,” absorbed as a vesicle-like structure, through intestinal M cells, through a paracellular or intracellular way [7].

Sodium ferric gluconate (SFGC) is the cheapest and a safe formulation of intravenous iron currently on the market. Each 5-ml vial contains 177 mg of SFGC, corresponding to 62.5 mg of trivalent elemental iron.

The aim of the current study was to verify whether high doses of SI are as safe, effective, cheap, and well tolerated as the standard SFGC intravenous doses in patients with iron deficiency anemia, without significant comorbidities.
Patients and methods

This study is a prospective multicentric study. Patients were enrolled from 3 centers: two regional hospitals and one regional family medicine service. Time of enrollment was 20 months.

Demographic characteristics of the enrolled patients are listed in Table 1. The median follow-up was 12 months (range, R: 8–18).

Patients were consecutively randomized (random 1:1) to receive oral Sucrosomial iron (SI) or i.v. sodium ferric gluconate.

In group A, patients received Sucrosomial iron (Sideral® Forte) 30-mg tablet 2 tabs twice daily for 1 month; for the first 15 consecutive days, iron was taken without food; and for the following 15 days with food, with or without antiacid therapy.

In group B, patients received sodium ferric gluconate 1 vial (62.5 mg) in normal saline solution (ns) 250 ml intravenous (i.v.) under continuous infusion (ci) in 3 h/day. The number of required vials was calculated with the adapted formula: (0.65 × body weight in kg) (12-Hb g/dl) × 3.3 × 1.5 / 62.5 [8, 9].

The study was carried out in accordance with the provisions of the Declaration of Helsinki and local regulations. Informed consent was obtained from each participant. The protocol was approved by the institutional review boards of all the enrolling centers.

Inclusion criteria were age > 18 years, no other established causes of anemia, hemoglobin < 10 g/dl, ferritin < 30 ng/ml, total iron binding capacity saturation < 20%, iron sulfate intolerance, failure to increase 1 g of hemoglobin (Hb) after 1-month treatment with iron sulfate at a dosage of 660 mg (2 tabs)/day, failure of normalization of the Hb level after 3 months of 660 mg of iron sulfate (2 tabs), at least one positive sample of fecal occult blood test out of three with esophageal gastro-duodenoscopy and pan colonoscopy negative for neoplasia, non-neoplastic hypermenorrhea, and/or menometrorrhagia, gastric bleeding (ulcer, gastritis, angiodysplasia), small intestine bleeding (angiodysplasia, ulcer), and colorectal bleeding (diverticulitis, angiodysplasia, hemorrhoids).

Exclusion criteria were loss of 1 g Hb/dl within a timeframe of less than 7 days, hyperthyroidism, severe chronic heart failure, autoimmune disease, inflammatory bowel disease, ischemic/hemorrhagic enterocolitis, neoplasia with or without active treatment, helminthic infestation, erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) increase, pregnancy/breastfeeding, and severe organ failure.

The median cost of treatment in each group was calculated taking into account the overall cost of all therapy for each patient during the observation period, then dividing this cost for the months of follow-up to obtain average cost per month of follow-up per patient. In each group, the median of the average cost per month of follow-up per patient was then calculated. This provides a valuation of the costs, unrelated to the exact cost of the drug, but linked to the outcome and efficacy of the therapeutic strategy during the observation period.

Details of the calculated costs are reported in Table 2.

Table 1 Patients’ characteristics

|                  | Group A       | Group B       | p   |
|------------------|---------------|---------------|-----|
| N                | 45            | 45            |     |
| M/F              | 2/3           | 2/3           | n.s.|
| Median age (years) | 75 (R: 35–85) | 62 (R: 40–83) | 0.02|
| Age > 80 years old | 14           | 5             | 0.04|
| Gastric bleeding | 15            | 18            | n.s.|
| Intestinal bleeding | 8             | 6             | n.s.|
| Menometrorrhagia | 22            | 21            | n.s.|
| Median Hb (g/dl) | 8.5 (R: 6.5–10) | 8.2 (R: 7.5–9.5) | n.s.|
| Ferritin (ng/ml) | 5 (R: 3–21)   | 7 (R: 2–19)   | n.s.|
| Iron sulfate intolerance | 18    | 7             | 0.02|
| Iron sulfate ineffectiveness | 22    | 30            | n.s.|
| Median days of dark stools | 5 (R: 2–12) | 6 (R: 1–8)   | n.s.|
| Pat. with > 7 days of dark stools | 5    | 2             | n.s.|
| No. of patients taking PPI | 20   | 21            | n.s.|
| Median dose of elemental iron received (mg) | 3360 (R: 2800–3600) | 640 (R: 520–780) | < 0.01|

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Evaluation of perceived quality of life was performed by administering the SF-8™ questionnaire, a generic multipurpose short-form health-related quality of life instrument, developed by the RAND Corporation and the Medical Outcomes Study (MOS).

A numerical rating scale (NRS) between 0 and 10 was used to assess pain intensity (0: no pain, 10: the worst pain ever possible) [10].

The degree of diarrhea was classified according to the NCI Common Toxicity Criteria (CTC) scale, version 3.0.

The following assays were weekly performed: complete blood count, B12, folates, haptoglobin, blood iron, ferritin, total iron binding capacity, liver enzymes, creatinine, blood urea nitrogen, C-reactive protein in the first 6 weeks of the study. All these tests were performed monthly during the entire follow-up period with fecal occult blood test.

We analyzed differences between clinical parameters among 90 patients to evidence any possible association and significant difference. Depending on distributions, variables were described as mean and median. To compare distributions between groups, we used one-way ANOVA and post hoc comparisons were performed with the unpaired-samples t test, Mann-Whitney test, or chi-square test, as appropriate; in all cases, we used a Bonferroni correction. The chi-square test was computed with Yates’ continuity correction for 2 × 2 contingency tables. A p value < 0.05 was considered statistically significant.

Results

The median number of sodium ferric gluconate vials administered was 10 (R: 8–12). Days needed to reach a 1-g/dl increase of hemoglobin levels from basal level were 9 days (R: 7–15) in group A (Sucrosomial iron) vs 7 days (R: 6–11) in group B (SFGC) (p n.s., Fig. 1).

Weeks required to achieve an Hb target value of 12 g/dl were 4 (R: 2–4) in group A vs 3.5 (R: 1.5–4) in group B (p n.s., Fig. 2).

In the group of patients taking oral Sucrosomial iron without food, 7 (16%) complained of stomach pain (NRS evaluation: 2 patients = 4, 2 patients = 3, and 3 patients = 2) and 5 (11%) diarrhea (3 patients = G2, 2 patients = G1) (Table 3). All patients complaining side effects were 80 years old or more. When patients took Sucrosomial iron with food, 2 (5%) complained burning stomach pain (NRS evaluation = 2) and 2 (5%) diarrhea (NCI scale = G1).

In the SFGC group, 5 (11%) patients showed hypotension and 5 urticaria and headache. Only 2 patients complaining side effects were older than 80 years.

The highest total monthly median expenditures, accounting for 300 Euros, were reported in patients treated with SFGC, compared to patients supplemented with SI (p < 0.001), accounting for 120 Euros. Although the unitary cost of a Sideral® pill box seems to be higher than that of a vial of Ferlixit® (EUR 20 per Sideral® box vs EUR 0.95/vial for i.v. iron), the highest direct (EUR 35 for doctor visit, EUR 35 for daily hospital admission, EUR 10 for outpatient hospital visit) and indirect (EUR 120 for a working day loss) costs were seen in the SFGC group, with a significant statistical difference (p = 0.013).

Table 2  Calculated costs of iron treatment

| Cost                                | Amount (€) |
|-------------------------------------|------------|
| CBC + blood tests + iron balance + B12 + folates + disposable materials (needle + gauzes + test tube + disinfectant) + ticket | 70         |
| Effluent                            | 0.43       |
| Normal saline 250 cc                | 0.90       |
| Gauzes                              | 0.01       |
| 1 day of day hospital stay (including nursing care and meals) | 200        |
| Medical care for 1 day of day hospital | 140        |
| 1 working day lost                  | 584        |
| Ticket for medical outpatient visit | 25         |
| Fee for outpatient examining room   | 16         |
| Cost 1 U PRBC or PLT                | approximately 200 |
| Cost 1 tablet Sucrosomial iron      | 1          |
| Cost 1 sodium ferrigluconate vial   | 1.2        |

Fig. 1 Days needed to obtain Hb 1-g/dl increase from basal level. iron gluc, sodium ferrigluconate; sucrosom, Sucrosomial iron

Fig. 2 Days needed to achieve Hb 12-g/dl target level. iron gluc, sodium ferrigluconate; sucrosom, Sucrosomial iron
At SF-8 evaluation, patients receiving SI showed a score of 58 vs 42 in the SFGC group; thus, a better quality of life and wellness perception was recorded in the SI group.

At a median time of 12 months after enrollment, the median value of ferritin (ng/ml) at end of treatment was 260 (R: 150–320) in the SI group vs 18 (R: 5–56) in the SFGC group (p = 0.01).

Seventeen (37%) patients in the SI group and 16 (35%) in the SFGC group (p n.s.) showed at least 3 fecal occult blood tests positive during the follow-up period, after the first 6 weeks of study.

Fifteen (33%) patients in the SI group and 10 (22%) in the SFGC group (p n.s.) showed at least 3 increased values of C-reactive protein with respect to the normal range during the follow-up period, after the first 6 weeks of study.

Table 3  Reported side effects following iron administration

|                          | Sucrosomial iron w/o food | Sucrosomial iron with food | SFGC |
|--------------------------|---------------------------|----------------------------|------|
| No. of patients with side effects/total | 12/45 | 4/45 | 10/45 |
| Patients with side effects ≥ 80 years old/total | 12/45 | 4/45 | 2/45 |
| Stomach pain              | 7 | 2 | 0 |
| Diarrhea                  | 5 | 2 | 0 |
| Hypotension               | 0 | 0 | 5 |
| Headache                  | 0 | 0 | 5 |

Discussion

IDA is a public health problem affecting 32.8% of premenopausal and 40.1% of pregnant women, 41.7% of growing children [1], between 13 and 90% of patients with various medical diseases [11–18], and 30% of elderly people [19]; furthermore, approximately two-thirds of patients undergoing major surgery develop postoperative anemia [20–22].

The real limit of oral iron supplements is their absorption. In fact, it happens like through a funnel. The heme-iron is absorbed by a heme transporter [23], ferric iron is absorbed by the DMT1 (divalent metal transport 1) transporter [24–28], lactoferrin binds iron through a lactoferrin-binding protein/receptor [29–31], and ferritin iron can be taken up via an endocytic process in Caco-2 cells (which have some enterocyte-like characteristics) and probably also in vivo [32–34]. All these iron carriers can be heavily upregulated, as DMT1, up to 4–12-fold during iron deficiency anemia and erythropoietin increase [35, 36]. However, these receptors, also when upregulated, allow a limited iron absorption. The iron efflux from enterocytes is regulated by ferroportin that likely allows a maximum increase in iron absorption of 3–4 folds, as seen in thalassemic patients [37, 38]. Moreover, in iron-deficient patients, the administration of oral iron sulfate causes an increase of serum hepcidin, a hormone blocking ferroportin and protecting against iron overload, that falls to basal levels 48 h after treatment, thus imposing an every-other-day administration schedule for an optimal iron absorption [39].

A typical Western diet provides about 15 mg of iron per day and only 10% of it is absorbed [36]. Recovery from blood loss causes an increase in iron absorption in the duodenum up to 20-fold. Patients with severe IDA or with normal iron stores receiving erythropoietin can absorb up to 20 to 40 mg/day of iron and the amount decreases when Hb levels increase [40, 41].

Oral iron is a cheap and effective way of correcting the marten deficiencies in patients without comorbidities, when iron loss exceeds the iron amount absorbed through food in the small intestine.

The cheapest commercially available oral iron formulation in Italy is iron sulfate. It is absorbed via a DMT1 transporter localized in the duodenal enterocyte brush border. Each tablet contains 325 mg of iron salts, containing 65 mg of elemental iron [35, 42]. However, gastrointestinal side effects are common [9, 43, 44]. It is estimated that 30% or more of patients taking iron-containing oral preparations develop gastrointestinal symptoms like nausea, constipation, diarrhea, dark stools, epigastric pain, and vomiting [45–47]. Gastrointestinal symptoms are proportional to the amount of elemental iron ingested [48].

Sucrosomial® iron is a new oral iron formulation, in which ferric pyrophosphate is protected by a phospholipid bilayer membrane composed mainly by sunflower lecithin, enveloped in a sucrester matrix stabilized by other ingredients as tricalcium phosphate and starch, forming the “sucrosome,” absorbed as a vesicle-like structure, through intestinal M cells, through a paracellular or intracellular way, bypassing the conventional iron DMT-1 absorption pathway [7, 49, 50]. Each tablet contains 30 mg of pyrophosphate iron.

The use of intravenous (i.v.) iron is indicated in patients intolerant to oral iron or when there is a problem of iron absorption (as in celiac disease, inflammatory bowel disease, gastric bypass, chronic inflammatory disease, cancer chemotherapy) or when intestinal blood losses exceed the ability of the normal duodenum to absorb ingested iron (as in obstetrics or surgical blood loss or in Osler-Weber-Rendu syndrome), because it bypasses mechanisms of duodenal absorption and increases Hb levels more quickly than oral iron [51–55].
In the current study, it is noteworthy that the number of days required to achieve a 1-g increase in hemoglobin levels after enrollment and the time to reach target hemoglobin level of 12 g/dl is practically identical in the two treatment groups. It seems that for the SI group, the iron given in the Sucrosomial formulation bypassed all the usual absorption mechanisms present in the brush border membrane of enterocytes, behaving, therefore, almost like the SFGC delivered parenterally.

This result is in open contrast to what would be expected by administering any other oral iron formulation. For example, we can consider the case of oral iron sulfate. The median amount of iron needed to achieve an increase of 1 g/dl of hemoglobin based on the aforementioned formula would be 225 mg. Considering that each iron sulfate tablet contains 65 mg of elemental iron, of which a maximum of 25 mg is absorbed, and that the optimal administration schedule is 1 tablet every other day, 18 days of treatment would be needed to theoretically achieve the desired goal vs 9 days in the SI group and 7 days in the SFGC group. Furthermore, to achieve the target Hb level of 12 g/dl in 72 days of treatment with iron sulfate should be needed vs 28 days in the SI group and 24 days in the SFGC group.

Some doubts can arise from the high amount of elemental iron received in the SI group in a month; in fact, it could potentially cause hemosiderosis. However, if we consider that the quantity of elemental iron necessary to reach the median level of 12 g/dl of hemoglobin, reached in 1 month in the SI group, is a median of 900 mg, that the median continuous loss of hemoglobin in each patient was 2 g/dl per month, corresponding to a median of 450 mg of elemental iron, and that 1000 mg of iron is needed to replenish martial stocks, the total median iron needed is 2350 mg. Moreover, in feces, humans loss about 13% of lipid needed to replenish martial stocks, the total median iron needed is 2350 mg. Considering that each iron sulfate tablet contains 65 mg of elemental iron, which a maximum of 25 mg is absorbed, and that the optimal administration schedule is 1 tablet every other day, 18 days of treatment would be needed to achieve the desired goal vs 9 days in the SI group and 7 days in the SFGC group. Furthermore, to achieve the target Hb level of 12 g/dl in 72 days of treatment with iron sulfate should be needed vs 28 days in the SI group and 24 days in the SFGC group.

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Results in patients taking proton pump inhibitors (PPIs) were superimposable, without statistically significant differences, to those not taking PPIs in each treatment group. This is in contrast with the evidence that proton pump inhibitors affect iron absorption, at least for the SI group [57–61].

Gastrointestinal side effects, mainly of low level, were reported in 27% of patients from the SI group, in accordance with data already reported in the literature [47]. It is not surprising that the totality of patients with side effects are 80 years old or older. In fact, 40% of elderly patients show gastrointestinal side effects [48, 62] and probably the high number of octogenarians with gastrointestinal side effects is only due to the low number of patients in our study. On the other hand, it is noteworthy that in patients taking Sucrosomial iron with food, gastrointestinal side effects are reduced to almost one-third (only 10%), a markedly lower percentage in comparison to previous studies.

Equally important is the fact that the administration of Sucrosomial iron with food does not impair its absorption, as shown by the same effectiveness of intravenous iron. In fact, usually, when oral iron formulation is given with food, its absorption is impaired by calcium, polyphenols, phytates, eggs, or soy contained in aliments [63].

ID, in which IDA is included [64], causes physical productivity reduction and cognitive and physical disability with an economic loss quantified, in 2002, as an absolute dollar value of $4.2 billion annually (corresponding to € 3.8 billion), with reference only to physical productivity losses in South Asia [64]. Economic loss secondary to ID has been estimated, in 2019, as CHF 78 million (€ 73.12 million) for direct medical costs and between CHF 26 million (€ 24.37 million) and CHF 33 million (€ 31 million) in a Swiss female population [65, 66].

The economic evaluation of SI treatment–related costs in the current study showed a possible cost saving, translated into a 60% abatement of overall monthly expenditures per patient compared to the SFGC group. Indeed, although the treatment cycle with Sucrosomial iron had higher purchase costs compared to i.v. iron, it greatly reduced other direct clinical expenditures (cost minimization) for the hospital and the public healthcare system as well as indirect costs. The information acquired by comparing the costs of the two different therapies confirms what our group has already observed in the context of myelodysplastic syndromes. In that case too, the high number of hospital admissions resulted in an increase in indirect costs and losses deriving from patients’ absences from work [67].

Moreover, a warning issued by the EMA and by the Italian Drugs Agency (AIFA) advises against the use of i.v. iron outside hospital with an intensive care unit, given the potentially fatal side effects linked to i.v. hypersensitization [68]. This imposes SFGC administration only in hospital, considerably worsening quality of life of patients receiving SFGC and explaining the higher value of perceived quality of life in the SI group.

Authors’ contributions GC conceived the study, wrote the first draft of the paper, and critically revised the manuscript. MN wrote the last version of the manuscript and equally contributed with GC to the current manuscript. AL, VDB, MN, and GC enrolled patients in the study. AL and VDB analyzed data and elaborated results.

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Data availability All data related to this study are available on request.

Compliance with ethical standards

Conflict of interest MN acted as the consultant for Bayer, BIOFVIIIx, Novonordisk, and Amgen, and received speaker fees from Kedrion,
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