Case Study Eurofer IV

Effects of individually dosed intravenous iron administration in patients with iron deficiency (Swiss Iron System SIS)

Multicenter postmarketing surveillance

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Summary

Goal: To document the effect of intravenous iron substitution in women with symptomatic iron deficiency with and without anemia: changes in symptoms, ferritin, hemoglobin, adverse effects and cost efficency.
Design: A multicenter case study involving the use with two different iron compounds (iron sucrose vs. ferric carboxymaltose).
Study centers: Twenty-nine medical practices (26 in Switzerland and three in Germany).
Participants: 2168 female patients receiving individually tailored intravenous iron substitution, 77% of whom were premenopausal.
Parameters evaluated: Changes in symptoms and laboratory values two to three weeks and three months after intravenous iron substitution.
Results: All participants completed the therapy. In 85% of the patients, the initial ferritin value was <50 ng/ml and in 15% between 51-75 ng/ml (average 30ng/ml). 12% of the participants had anemia. 65% of the participants felt better or were completely asymptomatic after treatment, 20% had partial symptomatic improvement and 15% had no improvement at all. At a follow-up evaluation three months later, the benefit was still evident although the mean ferritin value in premenopausal women had fallen to 143 ng/ml. The rate of adverse effects was less than 5%.
Conclusions: Patients with symptoms such as fatigue, difficulties in concentration, depressed mood, sleep disturbances, dizziness or headaches and a ferritin level less than 75ng/ml profited substantially from individually tailored intravenous iron substitution.

Introduction

Iron deficiency is the most common nutrient deficiency in humans. According to the World Health Organization (WHO), two to three billion people suffer from iron deficiency, of whom approximately half have no anemia. The characteristic symptom of fatigue is often attributed to iron deficiency anemia. Reliable studies evaluating the relationship between fatigue and iron deficiency in the absence of anemia are correspondingly rare.

The Iron deficiency syndrome with the cardinal symptom of fatigue (in the absence of anemia), which was rediscovered in Switzerland in 1998, was first described in 1957 at the University of Innsbruck, Austria (2) and was confirmed in 1971 at the Charité Hospital of the Humboldt University of Berlin, Germany (3). In 2003 at the University of Lausanne, Switzerland, it was shown that iron substitution even in iron-deficient patients without anemia was effective (4).

The Swiss Iron Health Organisation (SIHO) (21), founded in 2007, differentiates between three stages of iron deficiency: 1. asymptomatic iron deficiency without anemia = (AID); 2. symptomatic early stage iron deficiency = iron deficiency syndrome (IDS); 3. late stage iron deficiency = iron deficiency anemia (IDA). In one European study, it was shown that the ferritin level in 20% of premenopausal women was under 15 ng/ml, although only 4% of these women had anemia (5).

It is not known how many iron deficient women without anemia are symptomatic. We evaluated the response rate, tolerability and cost efficiency of individually tailored iron substitution therapy in women with the typical symptoms of iron deficiency (as much as needed and as little as possible).

Methods

This was a multicenter observational study. Data collection was carried out at 29 medical centers (26 in Switzerland and three in Germany) with a total of 2168 female patients observed. The course of therapy was documented between March 2006 and June 2011 as part of a prospective case study of medication usage using an internet database (Health-Banking) together with an integrated dosage-calculation formula and benefit analysis tool (quality management).

Inclusion criteria were patients with iron deficiency symptoms and a measured ferritin value < 75 ng/ml. The symptoms were categorized according to the clinical IDS score for determining the need for intravenous iron therapy. In contrast to the study done in Lausanne in 2003 (4), patients with psychiatric or other somatic symptoms and chronic fatigue syndrome, were included in this observational study.

The symptoms were divided into the four groups according to their frequency.

Clinical IDS-Score

Groupe 1:	Fatigue
Groupe 2:	Difficulties in concentration, depressive mood, sleeping disorders
Groupe 3:	Dizziness, heacache, neck tension
Groupe 4:	Hair loss, nail fragility, restless legs

Other potential causes of fatigue (for example diabetes mellitus, thyroid disorders or vitamin deficiencies) were excluded. Before starting Treatment (T1) we measured the ferritin-concentration. In order to more precisely characterize the iron deficiency, two other parameters of iron metabolism were measured: transferrin (TF) and soluble transferrin receptor (STR). A ratio of at least 1.5 from the average value of TF and LTR / log ferritin confirmed the diagnosis. Both of these indicators were used in calculating the dose.

The patients received one of the two iron preparations that are available in Switzerland: either 200 mg iron sucrose twice a week or 500 mg ferric carboxymaltose once a week, until the total individually calculated dose had been administered. Two (iron sucrose) to three (ferric carboxymaltose) weeks after the last loading dose had been administered, a follow-up examination in order to document and assess the symptoms and laboratory values was conducted. (T2) Whenever possible, an additional follow-up examination was performed after three months. (T3) Not only could the sustainability of success be evaluated, but also the individually tailored dosages for maintenance could be determined from the obtained data.

A course of treatment was considered to be successful when the symptoms as determined by the patient and the physician were no longer present or had significantly improved (group 1) and the ferritin value was in the targeted range. Group 2 included patients with little improvement, group 3 patients without any improvement.

Laboratory analyses were performed using routinely available methods. Most of the ferritin measurements were done according to the WHO Standard IS94/572, used e.g. by Beckman Coulter (37). Most of the soluble transferrin receptor analyses were done according to the Roche standard (38). With this method, an internal reference preparation is used. A minority of the analyses for ferritin and soluble transferrin receptor were performed with other methods, causing method- related variance. The reason is the use of different antibodies and instruments, which can lead to variation between the methods. The measurement of transferrin has always been performed based on an international standard.

Statistical analysis was performed according to the biostatistical guidelines of the University of Zürich .

Results

A total of 2168 patients met the inclusion criteria and were given iron infusions. Of these, 1559 received 200 mg doses of iron sucrose and 609 received 500 mg doses of ferric carboxymaltose. All patients could be evaluated after treatment. 1472 of the patients could be further evaluated three months after treatment (1109 patients receiving iron sucrose and 363 receiving ferric carboxymaltose). The average age of the patients was 38 years. Ninety-six patients were younger than 15 years of age, with the average age of this group being 12 years.

Frequency of symptoms

Fatigue (87%) was the principal symptom in all age groups. Other frequently described symptoms were difficulties in concentration (55%), depressed mood (50%), neck tension (49%) and sleep disturbances (43%). Iron deficiency anemia was present in only 12% of the study participants (Figure 1).

Notable was the frequency of concentration difficulties in children, even when fatigue was excluded. Together with the other frequently occuring symptoms such as headache or sleep disturbances, this symptom complex bears a resemblance to those of attention deficit (hyperactivity) disorder (AD(H)D).

The number of concurrent symptoms increases until the age of 20 years (four symptoms on average) and then remains constant (between four and five symptoms).

Fatigue	87	
Concentration difficulties	56	
Depressed mood	50	
Neck tension	49	
Headache	49	
Dizziness	44	
Sleep disorders	43	
Anemia	12	

Figure 1) Frequency of symptoms (%) before treatment

Table 1 shows the frequency of the symptoms according to age group. Chronic fatigue was the primary symptom in all age groups and was usually accompanied by other symptoms (on average four). Only anemia was comparatively rarely present.

Table 1) Frequency of symptoms (%) prior to therapy according to age group.

Symptom	Frequency	<15 J.	15-20 J.	21-30 J.	31-40 J.	41-50 J.	>50 J.
	n = 2168 (100%)	n =94 (4%)	n = 215 (10%)	n = 401 (18%)	n = 531 (24%)	n = 623 (29%)	n = 304 (14%)
Fatigue	87% (n =1880)	81%	85%	85%	89%	88%	86%
Concentration difficulties (ADS)	56% (n = 1199)	69%	48%	51%	58%	57%	53%
Depressed mood	50% (n = 1082)	38%	42%	47%	57%	53%	44%
Neck tension	49% (n = 1059)	18%	40%	49%	53%	53%	48%
Headache	49 (n = 1043)	38%	48%	47%	53%	50%	40%
Dizziness	44% (n = 938)	41%	40%	45%	47%	43%	37%
Sleep disorders	43% (n = 929)	35%	38%	35%	41%	48%	52%
Anemia	12% (n = 252)	9%	12%	11%	12%	13%	9%

Of the 2168 patients treated, 85% had an initial ferritin value of <50 ng/ml (44% with <25 ng/ml and 41% between 25-50 ng/ml). In 15% of the patients, the ferritin value was between 51-75 ng/ml (Figure 2). The average ferritin value before treatment was 30 ng/ml, a level also described by Favrat *et al.* (4).

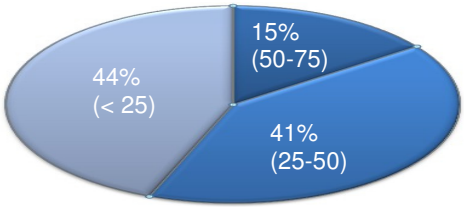

Figure 2) Ferritin values (ng/ml) in patients with iron deficiency prior to treatment (%)

The frequency of the symptoms was hardly influenced by the ferritin level, except in the case of anemia. Anemia was present significantly more often when the ferritin value was under 25 ng/ml (p< 0.0001).

Success rates

The changes in symptoms from the patients' and physicians' points of view are illustrated in Figure 3. It is striking to observe that there was a 65% probability that the symptoms disappeared or at least improved (confirmation of the diagnosis). Twenty-one percent of the patients felt somewhat better but still needed further evaluation and treatment. Only 14 % felt no symptomatic improvement. The success rate in patients with and without anemia was the same regardless of whether they were treated with iron sucrose or ferric carboxymaltose.

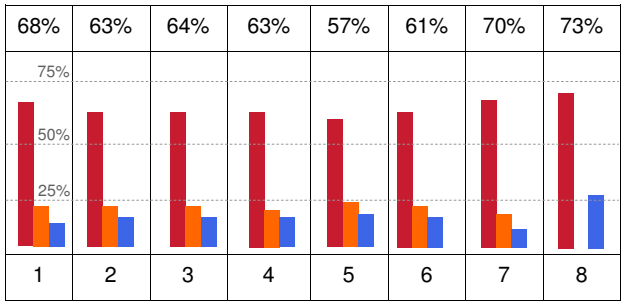

Figure 3) Success rate (%) after individually tailored intravenous therapy (T2) (% success)

1. Fatigue / 2. Concentration difficulties /
3. Depressed mood / 4. Sleep disorders /
5. Neck tension / 6. Headache / 7. Dizziness /
8. Anemia

Red bar: successfull treatment: symptom-free or marked improvement with percentage indications
Yellow bar: some improvement
Blue bar: unchanged

The number of patients who were asymptomatic or had definite improvement in their symptoms remained similiarly high at the three-month follow-up period (Figure 4).

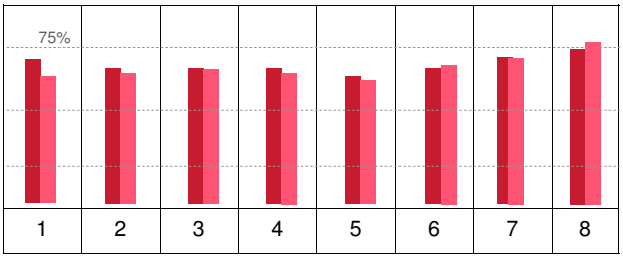

Figure 4) Successfully treated patients after individually tailored intravenous iron therapy (after treatment and three months later).

1. Fatigue / 2. Concentration difficulties /
3. Depressed mood / 4. Sleep disorders /
5. Neck tension / 6. Headache / 7. Dizziness /
8. Anemia

Red bar T2: first follow-up examination after treatment.
Pink bar T3: second follow-up examination three months after treatment.

Our study shows that the success rate in patients with an initial ferritin value of 50-75 ng/ml is on average 15% lower than that of patients with a value below 50 ng/ml (Figure 5). The success rates in patients with an initial ferritin of <25 ng/ml and those with values of 25-50 ng/ml does not differ significantly (68% vs. 66%).

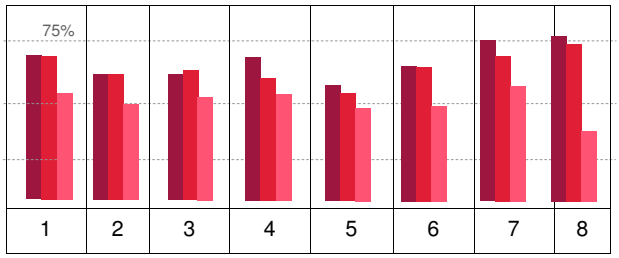

Figure 5) Success rate (%) is correlated with pre-treatment ferritin values.

1. Fatigue / 2. Concentration difficulties /
3. Depressed mood / 4. Sleep disorders /
5. Neck tension / 6. Headache / 7. Dizziness /
8. Anemia

Dark red bar: Success rate with initial ferritin value < 25 ng/ml
Red bar: Success rate with initial ferritin value 25-50 ng/ml
Pink bar: Success rate with initial ferritin value 50-75 ng/ml

Change in ferritin values after treatment

The average ferritin value was 30 ng/ml before treatment (T1), 222 ng/ml two to three weeks after treatment (T2), and 143 ng/ml, correspondingly lower, after three months (three menstrual cycles) (T3). The kinetics of the ferritin values after therapy were dependent on the dose of each unit of infusion (Table 2). On average, the patients received 0.89 g iron (minimal 0.1 g, maximal 2.0 g).

Tab. 2 Changes in ferritin (ng/ml) after therapy

	Ferr. T1	Ferr. T2	Ferr. T3
Iron sucrose 0.2 g	31	199	135
Ferric carboxymaltose 0.5 g	28	279	167
Average	30	222	143

Adverse effects

Thirty-nine (1.8%) of the 2168 treated patients complained temporary adverse effects, such as gastrointestinal complaints, rash, flu-like symptoms or dizziness. In those receiving iron sucrose (200 mg per infusion), the rate of adverse effects was 1.2 % and those receiving ferric carboxymaltose (500 mg per infusion), the rate was significantly higher at 3.4% (p <0.001).

Iron Deficiency Syndrome (IDS) and Iron Deficiency Anemia (IDA).

In this study, 88% of the patients had no anemia, although the ferritin value in almost half of the patients was below 25 ng/ml. Table 3 shows the correlation between hemoglobin and ferritin values. Striking was the fact that with a ferritin value of 5-10 ng/ml, the average hemoglobin value was at the lower levels of normal but still fell within the accepted reference range. This is not surprising, since the definition of a low normal ferritin value was apparently not based on absence or presence of symptoms.

Tab. 3) Correlation between ferritin (ng/ml) and average hemoglobin values (normal levels in women: 12-16 g/dl).

Ferritin	1-5	5-10	10-25	25-50	50-75
Hb	11.2	12.3	12.9	13.3	13.3

Discussion

Definition and diagnosis of iron deficiency

This observational study confirms the success rate 65%) of earlier studies (2,3,4,10) as well as the double-blinded, randomized study from Krayenbühl *et al.* (35), to a large extent.

Fatigue is still too seldom attributed to iron deficiency (4). Patients have a tendency to believe that their symptoms are due to psychosocial stress factors and not to biological reasons (6,7,8). Physicians, on the other hand, tend to attribute chronic fatigue to emotional rather than somatic reasons (9).

Our findings demonstrate that it is common – although not in every case - to have several symptoms when iron deficiency is present, and that these may disappear after therapy with individually dosed iron substitution: 1. fatigue / 2. difficulties in concentration / 3. depressed mood / 4. sleep disturbances / 5. neck tension / 6. headache / 7. dizziness, and often additionally hair loss, nail fragility and restless legs.

It is basically clear that iron deficiency can be of significance in many different areas of medicine: headache and dizziness for the neurologist and pediatrician, fatigue and sleep disorders for the generalist, depression and difficulties in concentration for the psychiatrist, or neck stiffness for the rheumatologist. Ideally, physicians confronted with such a “complaint” should consider iron deficiency and question the patients about further symptoms of this entity. By doing so, a simple and curative treatment could be initiated more often.

A few studies indicated that even certain non-hematological, iron-dependent processes can be affected by deficient iron stores, such as enzyme synthesis or neurotransmitter metabolism (16,17,18).

The success rate of treatment in patients with ferritin values between 50 and 75 ng/ml is 15% lower than for those with levels below 50 ng/ml. This observation suggests that ferritin values over 50 ng/ml are more often associated with no symptoms and that the presence of symptoms similar to those seen with iron deficiency may be attributed to other causes. Only 14% of patients noted no change in symptoms after iron substitution therapy, indicating that their symptoms were not caused by iron deficiency.

Of the 2168 iron-deficient patients, only 12% were considered to be anemic. This shows that the diagnosis of clinical iron deficiency is not entirely dependent on the presence of anemia. The lowest acceptable ferritin level cannot be generally defined. The levels of ferritin that place the patient at risk for developing symptoms of iron deficiency lie, depending on the patient, between 10 and 75 ng/ml but may be higher in certain patients.

The results of ferritin and soluble transferrin receptors are due to different methods of analysis, unfortunately only partially comparable. The SIHO recommends for comparable Ferritinanalyzes the Beckman Coulter method, and for the determination of soluble transferrin receptors, the Roche method.

Treatment

We identified a high rate of treatment success of 65% when the correct amount of iron was individually calculated and administered in the appropriate single doses and time intervals.

Because of increased adverse effects with 0.5 - 1.0 g ferric carboxymaltose, the indication for administering higher single doses should be carefully evaluated. Treatment of IDS patients with 0.2 g iron sucrose infusions (twice a week) until attainment of the calculated total dose has been shown to have maximal effectiveness and was best tolerated. It would probably be wise to restrict the higher single doses to those patients with iron deficiency anemia, for whom ferric carboxymaltose was developed and clinically tested. This restraint is advisable as long as no long-term scientific comparative studies are available.

Disproportionality: After the administration of high-dose ferric carboxymaltose (for example, 2 x 500 mg) the ferritin level three weeks after the last dose is 40% higher than two weeks after the last dose of iron sucrose (5x 200mg). This is due to a “fleeding effect”, during which the more highly dosed iron requires more time to become available for the tissue and organs. Three months later, the disproportionality is still at 24%.

The new concept (Table 4) for diagnosis, therapy and prevention presented in this study (Swiss Iron System, SIS) (19) has been used since 2005 by specialized centers for treatment of iron-related disorders. It has been implemented in multiple centers and is monitored online with regards to efficacy, safety and cost efficiency. It corresponds to the procedures of the SIHO (20).

Tab. 4 Diagnosis and Treatment of Iron Deficiency

1. Clinical IDS-Score
2. Blood analysis
3. Differential diagnoses / Contraindications
4. Indication / Dosage calculation
5. Loading treatment (Saturation)
6. First follow-up examination (Evaluation of successfull treatment)
7. Second follow-up examination (Evaluation of sustainability)
8. Planning of the maintenance therapy

The results presented here are very similar to those that have already been published in 2006, 2008 and 2009, with increasing patient recruitment (21, 22, 23). The continued success confirms our knowledge that the early stages of iron deficiency can cause symptoms and be successfully treated.

Conclusion

The diagnosis of IDS is challenging and requires a sophisticated therapy and follow-up care. Depending on the severity of the symptoms intravenous iron therapy is the appropriate first-line therapy, even in the early stages of IDS. IDS is a diagnosis on suspicion. The treatment must base on the clinical state and evaluations of the laboratory. The diagnosis can be confirmed by follow-up examination after substitution therapy. Due to the frequent relapses of IDS, particularly in premenopausal women, individualized maintenance therapy after initial treatment is often necessary.

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