Journal of General Practice
ISSN: 2329-9126
Schaub et al., J Gen Pract 2019, 7:2
Research Article
Open Access

Effects of Individual Dosed-Intravenous Iron Doses in Patients with Iron Deficiency: A Multicentre Medicine-Application Monitoring System

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Abstract

Aim: Progress documentation of the intravenous substitution in women with symptomatic iron deficiency with and without anaemia: Changes in symptoms and ferritin and haemoglobin levels, adverse drug reactions.

Design: A multicentre observational study using two different preparations (iron sucrose versus ferric carboxymaltose).

Study centres: 27 medical practices in Switzerland.

Participants: 2288 patients gave individually-dosed intravenous iron doses, 82% of them of menstrual age.

Examined parameters: Change in symptoms and laboratory values 2-3 weeks following intravenous iron treatment and three months later.

Results: All participants completed the treatment. In 82% of the patients the initial ferritin level was <50 ng/ml and in 18%, it was between 51-75 ng/ml (average value 31 ng/ml). Anaemia was present in 13% of those affected. 65% of the participants felt symptom-free or significantly better, following treatment with an average ferritin level of 217 ng/ml, 20% benefited slightly and 15% did not feel any effects. After a follow-up assessment of a part of the patients three months later, the success rate was practically unchanged, although the ferritin level in women of menstrual age had retreated to 142 ng/ml. The side effect rate was 2.1%.

Conclusion: Patients with symptoms, such as e.g. states of exhaustion, concentration disorders, depressive moods, insomnia, dizziness or headaches and a ferritin level below 75 ng/ml benefit the most from individually-dosed intravenous iron doses.

Keywords: Iron deficiency without anemia; Ferritin; Anemia; IV Iron therapy; Fatigue; Ferric carboxymaltose; Iron Sucrose

Introduction

Iron deficiency is mankind´s most common deficiency disease. Pursuant to the World Health Organization (WHO), 3-4 billion persons are affected, with approximately half of them not presenting anaemia [1]. The leading symptom of exhaustion has so far only been attributed to iron deficiency anaemia. Reliable studies on the relationship between fatigue and iron deficiency without anaemia are therefore rare. The iron deficiency syndrome (without anaemia) with the leading symptom of exhaustion, was first described by the University of Innsbruck in 1957 [2] and confirmed in 1971 by the Charité of the Humboldt-University Berlin [3]. In 2003, the University of Lausanne also proved that iron supplements produce a positive effect on symptoms, even in iron deficiency patients without anaemia [4]. The Swiss Iron Health Organisation SIHO founded in Switzerland in 2007, and distinguishes three stages of iron deficiency.

1. **Asymptomatic iron deficiency without anaemia:** EoA,
2. **Symptomatic preliminary stage of iron deficiency:** Iron Deficiency Syndrome (IDS)
3. **Advanced stage:** Iron Deficiency Anaemia (IDA)

A European study demonstrated that 20% of women of menstrual age present ferritin levels below 15 ng/ml and only 4% of these women developed anaemia [5]. So far, it is unknown how many women suffering from an iron deficiency without anaemia present any symptoms at all. We investigated the success rates and tolerability of individually-dosed intravenous iron treatments in women with typical iron deficiency symptoms by applying the marginal benefit principle (as much as necessary and as little as possible.

Research Methodology

The data was collected in 27 medical practices throughout Switzerland, with a total of 2288 patients. The courses of therapy were documented in an internet database (Health banking) with an integrated dose calculation formula and a benefit assessment tool (Quality management), as part of a prospective drug application monitoring, between 2006 and 2019.

Inclusion criteria

All patients with iron deficiency symptoms, as well as simultaneously presenting ferritin levels below 75 ng/ml, were included in the application study. The symptoms were recorded before and after intravenous treatment, by applying the Clinical IDS Score. In contrast to the Lausanne study of 2003 [6], this application study included patients presenting mental or physical ailments, as well as a chronic fatigue

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Received August 04, 2019; **Accepted** September 04, 2019; **Published** September 12, 2019

Citation: Schaub B, V. Orelli F, Rothen C (2019) Effects of Individual Dosed-Intravenous Iron Doses in Patients with Iron Deficiency: A Multicentre Medicine-Application Monitoring System. J Gen Pract. 7: 372

syndrome. The symptoms were divided into four groups, pursuant to their frequency.

Clinical IDS Score:

Group 1: States of exhaustion.

Group 2: Concentration disorders, depressive moods, insomnia.

Group 3: Dizziness, headaches and neck tensions.

Group 4: Hair loss, nail fragility and restless legs.

Other causes of states of exhaustion (e.g. diabetic metabolism, thyroid disorders), were excluded. To confirm the evidence, two additional iron metabolism parameters were measured, which indicate the severity of the iron deficiency (transferrin TF and soluble transferrin receptors LTR). The indication was confirmed based on a quotient of at least 1.5 from the average value of TF and LTR/log ferritin. Both indicators were considered for the dose calculation. The dose-calculation was made according the formula 1152-11 × Ferritin (ng/ml) +52× LTR (mg/l)=mg of iron. The patients received either 200 mg iron sucrose twice weekly or 500 mg ferric carboxymaltose once a week, until the individually-determined total amount was reached. Two (iron sucrose) to three weeks (ferric carboxymaltose) after the last saturation infusion, a follow-up was performed to document and evaluate the symptoms and laboratory values. According to the possibility, an additional check was performed after a further three months. Based on the assessed data, it was not only possible to test the sustainability of the success, but also to determine the individual maintenance therapy to be established. Treatment is defined as successful if the symptoms have disappeared pursuant to the patients' and the treating physicians' opinion or have at least improved significantly (Figure 3) and, simultaneously, the ferritin level is within the therapeutic target range. At the same time, those patients are recorded for whom the treatment only helped a little (yellow column) or did not notice any changes (blue column). The laboratory analyses were performed with the available routine methods. The majority of the ferritin determinations were performed pursuant to the WHO Standard IS94/572, pursuant to Beckman Coulter. Most analyses concerning soluble transferrin receptors were performed pursuant to the Roche-standard, which, pursuant to experience, has proven to be the most frequently used. An internal reference preparation is used in this case. A minor part of the analyses for ferritin and for the soluble transferrin receptors were performed by way of other methods, the results of which may be subject to method-related scattering. The reason for this, in the case of ferritin, is due to the use of different and partly outdated standards, which can result in differences between the methods. There are still no international standards for soluble transferrin receptors. The transferrin determination was always performed pursuant to an international standard. The statistical evaluation was performed pursuant to the biostatistics guidelines of the University of Zurich, Switzerland.

Results

A total of 2288 patients met the inclusion criteria and were treated with iron infusions. 1583 of the patients received single doses of 200 mg iron sucrose (Venofer) and 705 patients single dosis of ferric carboxymaltose (Ferinject). All patients underwent a post-treatment check-up. 1659 patients were additionally checked three months later (1188 patients with iron saccharose, 471 with ferric carboxymaltose). The average age of the patients was 37 years. 93 patients were younger than 15 years with an average age of 12 years.

Frequency of symptoms

Exhaustion (78%) is the leading symptom of all age groups. Other frequently described symptoms are concentration disorders (50%), depressive moods (43%), headaches (42%), neck tensions (42%) or insomnia (39%). Iron deficiency anaemia was present in only 13% of the included iron deficiency patients (Figure 1). What is striking - apart from states of exhaustion - is- the frequency of concentration disorders in childhood. Together with the symptoms that also frequently arise, such as headaches or insomnia, this complex of symptoms could characterise AD (H)I, among other things. The number of simultaneous symptoms increases from an average of 3-4 symptoms to 4-5 symptoms by the age of 40). Table 1 shows the frequency of symptoms by age group. Chronic fatigue symptoms are the leading symptom in all age groups, usually accompanied by other symptoms. Only anaemia is comparatively rare. Of the 2288 treated patients, 82% had a baseline ferritin level of <50 ng/ml (42% <25 ng/ml and 40% between 25-50 ng/ml). In 18% of the patients, it was 51-75 ng/ml (Figure 2). The average ferritin level prior to treatment was 31 ng/ml. Thus we are at the same initial level as Favrat [7].

Rates of success

The changes in symptoms pursuant to the patients' and the treating physicians' opinion are displayed in Figure 3. It is remarkable that the symptoms disappeared or at least improved significantly with an average probability of 65% (confirmatory diagnosis). 20% at least felt slightly better; however, they still required a subsequent clarification and appropriate further treatment. Only 15% of those treated felt no change. The proportion of patients who became symptom-free or experienced a significant improvement in their symptoms is still significant among the post-treated patients three months later (Figure 4). It can be noted that the success rate in patients with an initial ferritin level of 50-75 ng/ml is on average 14% lower than in patients which level is below 50 ng/ml (Figure 5). The average success rates for patients with a baseline ferritin level of <25 and those with 25-50 ng/ml, however, hardly differ (68% and 65%, respectively).

Change in ferritin levels following treatment

The average ferritin level prior to treatment (T1) was 31 ng/ml, two to three weeks after treatment (T2) 217, ng/ml and three months (three periods) later (T3), correspondingly lower (average 142 ng/ml). The kinetics of the ferritin level as a result of the treatment depends on the dosage of the individual fusions (Table 2). On average, the patients received 0.87 grams (Venofer 0.83/Ferinject 0.95).

Side-effects

Of the 2288 treated patients, 49 (2.1%) temporarily reported

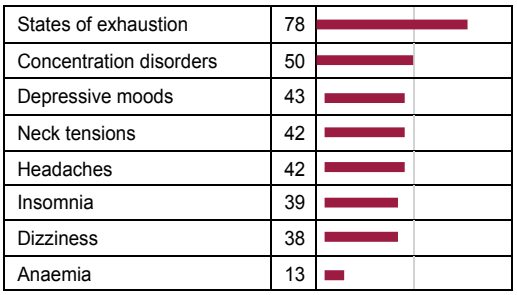


Figure 1: Frequency of symptoms (%) prior to therapy.

Symptoms	Frequency	<15 y	15-20 y	21-30 y	31-40 y	41-50 y	>50 y
	n=2288 (100%)	n=93 (4%)	n=236 (10%)	n=454 (20%)	n=594 (26%)	n=597 (26%)	n=314 (14%)
States of exhaustion	78% (n=1790)	80%	78%	76%	80%	78%	79%
Concentration disorders	50% (n=1133)	58%	44%	45%	51%	55%	46%
Depressive moods	43% (n=985)	38%	36%	43%	47%	44%	39%
Neck tensions	42% (n=967)	13%	37%	39%	48%	47%	40%
Headaches	42% (n=970)	37%	43%	43%	45%	44%	35%
Dizziness	38% (n=869)	35%	34%	39%	39%	40%	34%
Insomnia	39% (n=902)	32%	30%	36%	39%	45%	45%
Anaemia	13% (n=306)	14%	10%	14%	13%	15%	12%

Table 1: Frequency of symptoms (%) prior to therapy, correlated by age group.

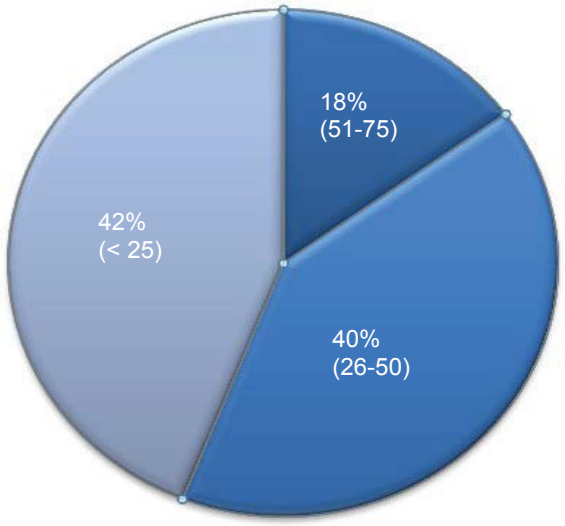


Figure 2: The ferritin level (ng/ml) in iron deficiency patients (%) prior to a saturation therapy.

undesired side-effects (such as gastrointestinal problems, skin rashes, flu-like conditions or dizziness). In iron-sucrose patients with 200 mg/infusion, the side-effect rate was 1.6 percent and in ferric carboxymaltose patients with 500 mg/infusion, significantly higher, at 3.4 percent ($p<0.01$).

Iron Deficiency Syndrome (IDS) and Iron Deficiency Anaemia (IDA)

A total of 87% of the patients did not present with anaemia, although the ferritin level was below 25 ng/ml at 42%. Table 3 displays the correlation between haemoglobin and ferritin levels. The fact that, with a ferritin value of 5-10 ng/ml, the haemoglobin is on average still in the lower standard, however, nevertheless within the reference range defined so far, is characteristic. The focus of such an approach is on preventing anaemia and not on avoiding symptoms.

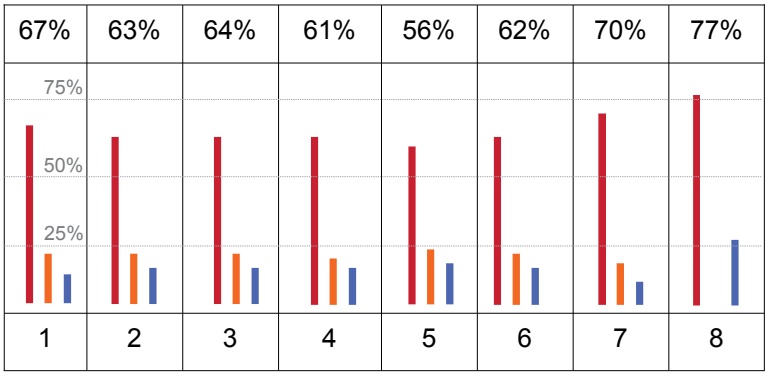
Discussion

The definition and diagnosis of iron deficiency

This case study confirms early studies [2-4], as well as the double-blind ranked study by Krayenbühl, success rate of 65%) to the greatest possible extent. Conditions of exhaustion are still too rarely attributed to iron deficiency [4]. The patients themselves often tend to attribute their complaints to psychosocial stress factors and not to biomedical causes [8]. Physicians, on the other hand, suspect that chronic fatigue is caused by emotional rather than physical factors [9-12]. Our observations have proven that several symptoms of iron deficiency occur very frequently, albeit not always, and can disappear by way of individually-dosed substitution: 1. Conditions of exhaustion; 2. Concentration disorders; 3. Depressive moods; 4. Sleep disorders; 5. Neck tensions; 6. Headache; 7. Dizziness, often hair loss, nail fragility and restless legs In principle, it can be stated that: Iron deficiency can be significant in many medical specialties: Headaches and dizziness at neurologists and paediatricians, exhaustion concentration disorders at the psychiatrist, depression and concentration disorders or neck tension at the rheumatologist. If the doctors were sensitised to the iron deficiency syndrome, additionally to each symptom complained about, they could inquire about additional symptoms, to complete the picture of an iron deficiency syndrome [13-15]. This would include the consequence that curative iron therapy could be initiated more frequently. Only a few studies indicate that non-haematological iron-dependent body functions can also be influenced by iron deficiency, such as enzyme formation or the metabolism of the neurotransmitters [16-18]. With ferritin levels between 50 and 75 ng/ml, the therapy success is 16% lower than in the case of levels below 50 ng/ml. This observation suggests that ferritin levels above 50 ng/ml are more often asymptomatic and iron deficiency reminding symptoms are caused by other factors. Altogether only 15% did not feel any change at all on account of the iron supplements. Thus, her symptoms were not due to the iron deficiency. Only 13% of the 2288 iron deficiency patients were identified as anaemic. This shows that the diagnosis of a manifest iron deficiency is by no means dependent on anaemia. A basic standard level of ferritin cannot be defined on a global basis. The basic "risk level" of ferritin for the development of iron deficiency symptoms is - depending on the patient - between 10 and 75 ng/ml, however, it may be even higher in individual patients. Unfortunately, due to the different measuring methods used, the results of ferritin and the soluble transferrin receptors can only be compared to a limited extent. SIHO recommends the Beckman-Coulter method for comparable ferritin analyses and the Roche method for the determination of soluble transferrin receptors.

Treatment

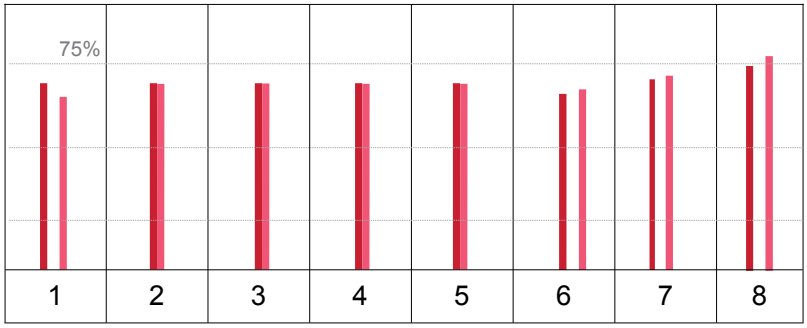
We could observe that, at a level of 85%, the success rate for treatment is high if the amount of the missing iron is calculated individually and supplied in suitable single dosages and intervals. Due to the increased rate of side-effects when 0.5 g ferric carboxymaltose is administered, we



1. Conditions of exhaustion; 2. Concentration disorders; 3. Depressive moods ; 4. insomnia; 5. Neck tensions; 6. Headache; 7. Dizziness; 8. Anaemia

Red column: successful: free of complaints or significantly improved with a percentage indication
Yellow column: slightly improved; **Blue column:** unchanged

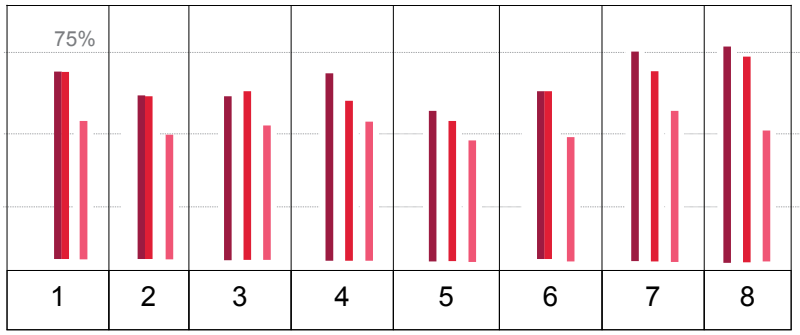
Figure 3: Success rates (%) after individually-dosed intravenous saturation with iron (T2) (% successful).



1.Conditions of exhaustion; 2. Concentration disorders; 3.Depressive moods; 4. Insomnia; 5. Neck tensions; 6. Headache; 7. Dizziness; 8.Anaemia

Red column T2: Initial post-treatment check following treatment
Pink column T3: Second post-treatment check three months later

Figure 4: Successfully treated patients after individually-dosed intravenous saturation with iron (following treatment and three months later).



1. Conditions of exhaustion; 2. Concentration disorders; 3. Depressive moods; 4. Insomnia; 5. Neck tensions; 6. Headache; 7. Dizziness; 8. Anaemia

Dark-red column: EQ for baseline ferritin level < 25 ng/ml

Red column: EQ for baseline ferritin level 25-50 ng/ml
Light-red column: EQ for baseline ferritin level 50-75 ng/ml

Figure 5: The success rates' EQ (%) correlates with the initial ferritin level.

Variables	Ferr. T1	Ferr. T2	Ferr. T3
Venofer 0.2 g	32	196	136
Ferinject 0.5 g	29	263	156
All	31	217	142

Table 2: Ferritin course (ng/ml) following a treatment.

Ferritin	1-5	5-10	10-25	25-50	50-75
Hb	10.9	12.1	12.9	13.2	13.3

Table 3: Correlation between ferritin (ng/ml) and average haemoglobin (average for women): 12-16 g/dl).

S. No	Diagnosis and treatment
1	Clinical IDS Score
2	Blood tests
3	Differential diagnoses/Contraindications
4	Indication/Dose calculation
5	Saturation therapy
6	Initial therapy control (Success control)
7	Second therapy control (Sustainability test)
8	Planning and calculation of maintenance therapy

Table 4: Diagnosis and treatment of the iron deficiency syndrome.

believe that the indication for high single doses should be reconsidered. The treatment of IDS patients with 0.2 g iron sucrose infusions (2 × per week) until the calculated total amount is achieved, has proven to be optimally effective and, at the same time, best-tolerated. It would therefore probably be advisable to reserve higher individual dosages for anaemic iron deficiency patients for whom ferric carboxymaltose has been developed. This restraint is recommended at least for as long as no comparative scientific studies are available.

Disproportionality

Following high doses of ferric carboxymaltose (twice 500 mg), the ferritin level, three weeks after the last infusion, is higher than two weeks after the last infusion of iron sucrose (five times 200 mg). The reason for this is the "flooding phase", during which the higher dosed iron requires more time to diffuse from the blood vessels and thus become available in the tissues and organs. The new concept presented in this application study (Table 4) for diagnostics, therapy and prevention (Swiss Iron System SIS) [19] has been applied in specially-trained medical iron centres since 2005 and tested for effectiveness, safety and cost efficiency with online monitoring. It corresponds to the instruments of the Swiss Iron Health Organisation SIHO [21]. The results presented herein are identical to those published in 2006, 2008, 2009 and 2015 (www.eurofer.ch) with an increasing number of patients [22], with minor deviations. This continuity of success further strengthens our understanding that the early stages of iron deficiency can be symptomatic, as well as successfully treated [23].

Conclusion

The diagnosis of IDS is demanding and requires planned therapy and aftercare. Depending on the level of suffering caused by the symptoms, intravenous iron therapy is the appropriate first-line therapy. The diagnosis can be confirmed by follow-up examinations after substitution therapy. Due to the frequent recurrences of IDS, especially in premenopausal women, individual maintenance therapy is often necessary following saturation therapy.

Acknowledgment

We thank all patients, doctors and nurses for their cooperation.

Financial Disclosure

This observational study was not supports by external funding sources.

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