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Comparison of the efficacy and adverse effects of oral ferrous succinate tablets and intravenous iron sucrose: a retrospective study

Yixin Li[1*] and Jing Ju[2]

Abstract

Objective To analyse the clinical efficacy and adverse drug reactions (ADRs) of iron preparations.

Methods A total of 374 patients with iron deficiency anaemia admitted to our hospital between 1 January and 31 December 2020 were included in this study. They were divided into 2 groups based on their medication regimens: Group A ($n=187$) took oral ferrous succinate tablets, and Group B ($n=187$) received intravenous iron sucrose. The remission of major symptoms, laboratory test results, ADRs and other related data were collected after 4 weeks of treatment.

Results Compared with the pre-treatment baseline, haemoglobin (Hb), serum iron (SI), serum ferritin (SF) and the mean corpuscular volume (MCV) increased in both groups at 4 weeks of treatment ($P<0.05$). After treatment, Group A had lower levels of Hb (108.41 ± 8.39 vs. 122.31 ± 6.04 g/L, $t=6.293$, $P<0.001$), SI (9.72 ± 4.24 vs. 15.62 ± 5.41 μmol/L, $t=5.482$, $P<0.001$) and SF (27.1 ± 10.82 vs. 39.82 ± 10.44 ug/L, $t=6.793$, $P<0.001$) compared with Group B. In contrast, there was no significant difference in the post-treatment level of MCV ($P>0.05$). The overall response rate significantly differed between the 2 groups (78.61% vs. 90.91%, $\chi^2=10.949$, $P<0.001$). The incidence of ADRs of both groups were similar, and the difference was not statistically significant ($\chi^2=0.035$, $P=0.851$).

Conclusion Iron sucrose demonstrates favourable efficacy and safety in treating iron deficiency anaemia.

Keywords Iron deficiency anaemia, Iron sucrose injection, Ferrous succinate tablet, Adverse drug reaction

*Correspondence:
Yixin Li
happyyixin9@163.com
[1]Department of Pharmacy, First hospital of shanxi medical university, No. 85 Jiefang South Road, Taiyuan City 030001, Shanxi Province, China
[2]Department of Colorectal and anal surgery, Shanxi provincial people's hospital, Taiyuan City 030001, Shanxi Province, China

Introduction

Iron is an essential trace element for the human body as it constitutes haemoglobin (Hb), which transports oxygen to tissues and organs for respiratory oxidation [1, 2]. Additionally, iron helps form various enzymes and compounds within the immune system [3–5]. It plays a role in promoting development [1], enhancing the immune system, regulating tissue respiration and maintaining normal blood colour in the skin [6]. The World Health Organization recommends an iron intake of 5–9 mg/day for adult men and 14–28 mg/day for adult women [6]. Iron deficiency and iron deficiency anaemia are global nutritional issues that need attention [7]. Supplementing an adequate amount of iron is fundamental to prevent and treat iron deficiency anaemia [8].

However, oral iron supplements exhibit high gastrointestinal adverse drug reactions (ADRs) (approximately 35–59%), long treatment cycles and poor absorption. This is mainly due to the inverse relationship between the absorbed amount of oral iron supplements and the iron reserves in the body. When serum ferritin (SF) exceeds 200 ng/mL or transferrin saturation is over 20%, red blood cells reach the optimal concentration, and the absorption of orally administered iron does not increase. The therapeutic effect of oral iron supplementation may be compromised for individuals with poor gastrointestinal tolerance or patients with chronic kidney disease. Therefore, researchers have developed intravenous iron preparations to enhance absorption [8, 9].

Currently, there are seven intravenous iron supplements available internationally for clinical use: high-molecular-weight iron dextran, low-molecular-weight iron dextran, sodium ferric gluconate, iron sucrose, sodium ferric gluconate, iron sucrose, ferric carboxymaltose, ferumoxytol and iron isomaltoside 1000 [10]. Iron dextran and iron sucrose are the only intravenous preparations available in the Chinese market. Despite their similar efficacy in treating anaemia, these two iron supplements differ in their ADR rates. Because iron dextran can cause significant ADRs, doctors and patients who use it perceive intravenous iron supplements as carrying higher risks. This perception leads to considerable challenges in promoting the use of newly developed intravenous iron supplements. Although the improved products reduce the risk associated with intravenous injections, the historically high incidence of ADRs to iron supplements continues to limit their practical application for various reasons, despite corrections made to traditional beliefs by the 2019 Chinese expert consensus on the application of intravenous iron [2].

Although medications are essential for treating diseases, they may induce serious ADRs. Statistics from the China ADR Monitoring Centre show that every year, ADRs cause approximately 192,000 deaths and contribute to nearly 2.5 million hospitalisation cases [11]. Some patients discontinue medication due to intolerance to ADRs, leading to reduced medication compliance [12]. Therefore, it is imperative to prevent or mitigate ADRs depending on the individual cases.

In the 1980s, China introduced its first regulatory system for ADRs: the Drug-Induced Toxicity and Side Effects Reporting System [13]. This system has been refined and developed over the years through increased international exchanges [14] and significant advancements in information technology for data management [15]. Consequently, there has been a substantial increase in the collected ADR data [16]. The proper use of this data can guide the implementation of necessary measures to reduce and prevent ADRs. Therefore, strengthening the monitoring of ADRs and their timely reporting, imposing practical measures and adjusting medications promptly can effectively reduce them. This study investigates the use of iron preparations and their ADRs.

Participants and methods

Study participants

This study aimed to analyse the clinical efficacy and ADRs of iron preparations. It retrospectively collected clinical data from 374 patients with iron deficiency anaemia admitted to our hospital between 1 January and 31 December 2020 using the convenience sampling method. The sample size was calculated using Group software with $\alpha = 0.05$ and statistical power ≥ 0.8, requiring a sample size of between 182 and 246. The retrospectively collected sample size was 374, which met statistical efficiency. Based on their medication regimens, the patients were categorised into Group A and Group B. Group A received oral ferrous succinate tablets ($n = 187$), and Group B was administered intravenous iron sucrose ($n = 187$). Due to the uncontrollable ADRs of iron dextran injections, which were not used in our hospital, these drugs are not discussed in the study.

The inclusion criteria were as follows: (1) aged ≥ 12; (2) iron deficiency, which was confirmed by ferritin examination; and (3) complete clinical data. The exclusion criteria were as follows: (1) severe primary diseases affecting the brain, liver, kidneys or hematopoietic system, which were confirmed through tests and examinations; (2) the presence of abnormal mental conditions; (3) patients with allergies to the study drugs; (3) patients with poor compliance or dependency issues; (4) participants in other clinical trials and individuals with conditions complicating or reducing the likelihood of inclusion. All the 374 patients mentioned in the method met the inclusion criteria. This study was approved by the hospital's ethics committee, and informed consent was obtained from all patients.

Research methods

Group A: patients in Group A were administered pure ferrous succinate tablets (0.1 g/tablet) (Hunan Jiudian Pharmaceutical Co., Ltd., G.Y.Z. Zi H20193239) at a dose of 0.2 g, twice daily. The tablets were taken after meals to alleviate local gastrointestinal irritation.

Group B: patients in Group B were treated with injectable iron sucrose (Nanjing Hencer Pharmaceutical Co., Ltd., G.Y.Z. Zi H20046043). The injection consisted of iron sucrose and 0.9% sodium chloride solution, with a concentration of 100 mg of iron sucrose in 5 ml of 0.9% sodium chloride solution, and was administered intravenously. The infusion rates were as follows: 100 mg over at least 15 min, 200 mg over at least 1.5 h, 400 mg over at least 2.5 h and 500 mg over at least 3.5 h. The iron supplementation amount (mg) was calculated as follows: body weight (kg) × (target Hb level − actual Hb level) (g/L). The total dosage of the product (ml) was calculated as follows: the total iron deficit (mg) divided by 20 mg/ml. The injection was administered intravenously at a dose of 5 ml, twice a week, based on individual body weight.

Data collection

The remission of major symptoms and laboratory test results were documented after 4 weeks of medication. Blood samples were obtained from each patient to analyse the levels of Hb, serum iron (SI), SF and the mean corpuscular volume (MCV). Efficacy was evaluated using the following criteria. (1) Complete response (CR): marked improvement in anaemia symptoms, with a rise in Hb of >30 g/L. Specifically, Hb should be >130 g/L for adult men and >120 g/L for adult women (>110 g/L for pregnant women). (2) Partial response (PR): visible improvement in anaemia symptoms, with an increase in Hb of >15 g/L despite a Hb level below normal. (3) No response (NR): no significant improvement in anaemia symptoms, with either no increase in Hb or an insignificant rise. The overall response rate (ORR) was calculated as follows: (CR cases + PR cases) / total number of cases × 100%.

Table 1 Comparison of general information between the two groups

Item	Group A (*n* = 187)	Group B (*n* = 187)	$\chi^2/t/z$ value	*p*-value
Sex (M/F)	89/98	94/93	0.268	0.605
Age (yrs, x ± s)	45.49 ± 6.99	46.87 ± 7.42	0.947	0.302
BMI (kg/m^2, x ± s)	23.98 ± 3.12	22.86 ± 2.41	1.322	0.210
Severity of anemia (n)			−1.628	0.103
Mild	48	35		
Moderate	132	143		
Severe	7	9		
Cause of anemia			0.246	0.970
Renal anemia	46	45		
Anemia during pregnancy	11	10		
Cancer-related anemia	18	16		
Other causes	112	116		

Statistical methods

Statistical analysis was conducted using the SPSS 26.0 software. The normality of measurement data was assessed using the Kolmogorov–Smirnov test. Normally distributed measurement data were presented as mean ± standard deviation (x ± s). The independent sample *t*-test was used to examine comparisons of means between groups, and the paired sample *t*-test was employed for intra-group comparisons. Enumeration data were expressed as frequencies (n) or percentages (%). The chi-squared test was used for conditions meeting the assumptions, and Fisher's exact probability test was employed for situations not meeting the assumptions. Data with skewed distributions were compared using the Kruskal–Wallis H rank-sum test. The significance level was set at $\alpha = 0.05$.

Results

General information

A total of 374 patients with anaemia were included in this study, with an age range of 12–80 years. Group A consisted of 187 patients, including 89 men and 98 women, with an average age of 45.49 ± 6.99 years. In Group A, there were 48 cases of mild anaemia, 132 cases of moderate anaemia and 7 cases of severe anaemia. In Group B, there were 187 patients, including 94 men and 93 women, with an average age of 46.87 ± 7.42 years. In Group B, there were 35 cases of mild anaemia, 143 cases of moderate anaemia and 9 cases of severe anaemia. No statistically significant differences were observed between the 2 groups in terms of gender, age, body mass index and the severity and cause of anaemia (all $P > 0.05$) (see Table 1).

Intra-group comparison of routine blood test results and iron metabolism before and after treatment

Before treatment, there were no statistically significant differences in Hb, SI, SF or MCV (all $P > 0.05$), suggesting good comparability between the 2 groups. Compared with pre-treatment levels, Hb, SI, SF and MCV levels significantly increased in both groups after treatment ($P < 0.05$). Following treatment, Group A exhibited lower levels of Hb (108.41 ± 8.39 vs. 122.31 ± 6.04 g/L, $t = 6.293$, $P < 0.001$), SI (9.72 ± 4.24 vs. 15.62 ± 5.41 μmol/L, $t = 5.482$, $P < 0.001$) and SF (27.1 ± 10.82 vs. 39.82 ± 10.44 ug/L, $t = 6.793$, $P < 0.001$) compared with Group B. In contrast, there was no statistically significant difference in MCV between the 2 groups after treatment ($P > 0.05$) (see Table 2).

Table 2 Within-group comparison of routine blood test results and iron metabolism before and after treatment

Item		Group A ($n=187$)	Group B ($n=187$)	*t*-value	*p*-value
Hb (g/L, x ± s)	Before treatment	71.12 ± 7.01	72.10 ± 7.01	0.768	0.512
	After treatment	108.41 ± 8.39	122.31 ± 6.04	6.293	< 0.001
	t/*p*-value	5.682/<0.001	6.545/<0.001		
SI (umol/L, x ± s)	Before treatment	2.40 ± 0.42	2.31 ± 0.42	0.423	0.675
	After treatment	9.72 ± 4.24	15.62 ± 5.41	5.482	< 0.001
	t/*p*-value	6.923/<0.001	4.692/<0.001		
SF (ug/L, x ± s)	Before treatment	11.42 ± 6.62	12.04 ± 6.79	0.911	0.315
	After treatment	27.1 ± 10.82	39.82 ± 10.44	6.793	< 0.001
	t/*p*-value	5.978/<0.001	6.592/<0.001		
MCV (x ± s)	Before treatment	67.5 ± 9.18	64.5 ± 7.84	0.788	0.504
	After treatment	85.31 ± 5.95	85.7 ± 5.18	0.007	0.933
	t/*p*-value	6.593/<0.001	7.895/<0.001		

Note: *Hb* haemoglobin, *SI* serum iron, *SF* serum ferritin, *MCV* mean corpuscular volume

Table 3 Comparison of response rates between the two groups

Group	PR	CR	NR	ORR (%)
Group A ($n=187$)	73	74	40	78.61%
Group B ($n=187$)	92	78	17	90.91%
χ^2-value				10.949
p-value				< 0.001

Note: *PR* partial response, *CR* complete response, *NR* no response, *ORR* overall response rate

Intra-group comparison of clinical efficacy

The results revealed that in Group A, there were 73 CR cases, 74 PR cases and 40 NR cases, totalling 147 cases responding to the proposed treatment. In Group B, there were 92 CR cases, 78 PR cases and 17 NR cases, totalling 170 cases responding to the treatment. There was a statistically significant difference in the ORR between the 2 groups (78.61% vs. 90.91%, $\chi^2=10.949$, $P<0.001$) (see Table 3). In this study, we focused specifically on patient populations with chronic kidney disease and cancer. Approximately 30% of patients in each group were diagnosed with these diseases. It is known that intestinal iron absorption is significantly affected in patients with chronic kidney disease and cancer due to the presence of inflammation. In our study, these patient groups showed a more pronounced improvement in efficacy after receiving intravenous iron therapy, which may be related to the negative impact of inflammation on iron absorption.

Intra-group comparison of adverse drug reactions

During treatment, both groups experienced ADRs, but no patient discontinued treatment because of them. The observed ADRs were mainly nausea, epigastric discomfort, phlebitis, reduced appetite, flushing and constipation. The ADR rate in Group A was slightly higher than that in Group B, but the difference was not statistically significant ($\chi^2=0.035$, $P=0.851$) (see Table 4).

Among all 31 patients experiencing ADRs, there were 10 men and 21 women. In the ADR reports for ferrous succinate tablets, 16 cases (100.00%) showed improvement. For iron sucrose injection-induced ADRs, 2 cases (13.13%) had an unknown outcome, 1 case (6.67%) showed no remission and the remaining (80.00%) either recovered or exhibited improvement, with no reported deaths.

Discussion

Anaemia is a common clinical symptom characterised by a decrease in the peripheral blood red cell volume below the lower limit of normal. Iron deficiency is a prevalent cause of anaemia, and various factors cause iron deficiency anaemia [17–19]. Regardless of the cause, the mainstay of treatment for anaemia involves iron supplementation. Due to insufficient understanding of intravenous iron preparations and the past high incidence of intravenous iron-induced ADRs, these preparations have limited use.

Ferrous succinate tablets are commonly used oral iron preparations in the current market, primarily indicated for iron deficiency anaemia of various origins, including chronic bleeding, pregnancy, malnutrition and developmental issues during childhood. Evidence has shown that

Table 4 Comparison of ADRs between the two groups

Group	Nausea	Epigastric discomfort	Phlebitis	Reduced appetite	Flushed	Constipation	ORR (%)
Group A ($n=187$)	3	2	0	3	4	4	8.56%
Group B ($n=187$)	4	1	5	2	3	0	8.02%
χ^2-value							0.035
p-value							0.851

Note: *ADRs* adverse drug reactions, *ORR* overall response rate

oral ferrous succinate tablets can significantly correct iron deficiency anaemia [20]. Iron sucrose is a complex with an average molecular weight of 43 kDa, comprised of a multi-nuclear iron (III) hydroxide core surrounded by non-covalently bound sucrose molecules. This large molecular structure prevents renal elimination and remains stable, with no release of iron ions under physiological conditions.

This study retrospectively collected clinical data from 374 patients with iron deficiency anaemia admitted to our hospital between 1 January and 31 December 2020 via the convenience sampling method. In terms of clinical efficacy, this study included 312 patients from special populations: 121 individuals with impaired renal function (including those undergoing haemodialysis), 57 children and adolescents, 21 pregnant women and 113 elderly individuals (excluding those with impaired renal function). In comparison with those using ferrous succinate tablets, iron sucrose users exhibited superior treatment outcomes, consistent with the findings reported by previous studies [21]. Moreover, approximately 30% of patients in each group had chronic kidney disease and cancer, which are well-known obstacles to intestinal iron absorption due to inflammation. This explains why the intravenous form is more effective. Notably, 101 patients with impaired renal function included in this study were diagnosed with chronic kidney failure, with the majority experiencing renal anaemia. In groups A and B, there were 46 and 45 patients with chronic kidney failure, respectively, all of whom received concurrent erythropoiesis-stimulating agents. Iron deficiency in renal anaemia not only exacerbates the severity of anaemia but also affects the effectiveness of erythropoietin. Following effective iron supplementation, the dosage of erythropoiesis-stimulating agents in both groups decreased compared with before treatment. The comparison of efficacy between the 2 groups indicates that intravenous iron supplementation can promptly and effectively replenish the iron required by patients with renal anaemia. It can also improve their condition safely and enhance the effect of erythropoiesis-stimulating agents using a reduced dosage.

Our results suggest that patients with chronic kidney disease and cancer benefit more from intravenous iron therapy than from oral iron therapy. This finding is consistent with reports in the literature that intestinal iron absorption is impaired in chronic inflammatory states [21–23]. Intravenous iron has been shown to have a higher efficacy in these patient groups due to its direct access to the bloodstream, bypassing the intestinal absorption step. In addition, the use of intravenous iron may also reduce gastrointestinal irritation, which is particularly important for patients with impaired gastrointestinal function. Therefore, our study emphasizes the need to consider the patient's specific pathological status when formulating clinical treatment strategies, and may require personalized treatment plans for patients with chronic kidney disease and cancer.

Iron sucrose-induced ADRs include metallic taste [22], headaches [23], nausea [24] and vomiting [25]. The incidence rates of these reactions are generally low. In this study, no severe ADRs were observed in either group, and no significant statistical differences were found between the groups. Among the 31 patients who experienced ADRs, damage to the skin and its appendages, the administration site and the gastrointestinal system ranked among the top three in terms of ADRs affecting systemic organs. Phlebitis at the administration site had the highest incidence rate among ADRs related to iron sucrose injection, occurring in 5 cases (33.33%). Previous research data shows that the incidence of phlebitis following intravenous injection of iron sucrose is approximately 11.1–50%, which is related to the number of injections. This might be because iron sucrose injection is a complex solution of multi-nuclear iron (III)-sucrose, which, upon entering the body through intravenous administration, dissociates into sucrose and iron in the reticuloendothelial system. This dissociation potentially stimulates local blood vessels [26], thereby elevating the risk of phlebitis during intravenous infusion [27, 28].

This study has certain limitations. First, it is a retrospective analysis, which may result in deficiencies in patient inclusion criteria, clinical data selection and data processing. Second, the study is confined to patients treated at our hospital, potentially introducing bias to the results. Further research with an expanded sample size is recommended for a more comprehensive investigation and data refinement and to provide more accurate real-world evidence for the effective prevention of ADRs. In addition, inflammatory markers were not collected in this paper, which is a limitation of this study. In further studies, we will collect inflammatory markers for subgroup analysis to evaluate their impact on the efficacy of iron supplementation.

Conclusion

This study compared the clinical efficacy, clinical parameters and ADRs of ferrous succinate and iron sucrose, indicating that iron sucrose is effective and safe in the treatment of iron deficiency anaemia. For patients with poor response to oral iron, intravenous injection of iron sucrose can effectively improve anaemia, providing supportive evidence for its clinical promotion and application. The results of this study highlight the potential advantages of intravenous iron in treating specific patient groups, particularly those with chronic kidney disease and cancer. Our findings support the importance of personalizing treatment for these patients and provide a

basis for future studies to further explore the use of intravenous iron in these patient groups.

Abbreviations

ADRs	adverse drug reactions
Hb	haemoglobin
SI	serum iron
SF	serum ferritin
MCV	mean corpuscular volume
CR	Complete response
PR	Partial response
NR	No response
ORR	overall response rate

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Author contributions
(I) Conception and design: Li YX and Ju J. (II) Administrative support: Li YX. (III) Provision of study materials or patients: Ju J. (IV) Collection and assembly of data: Li YX and Ju J. (V) Data analysis and interpretation: Li YX and Ju J. (VI) Manuscript writing: Li YX and Ju J. (VII) Final approval of manuscript: Li YX and Ju J.

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Data availability
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the declaration of Helsinki. This study was approved by the First hospital of shanxi medical university's ethics committee, and informed consent was obtained from all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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