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REVIEW ARTICLE

Efficacy and tolerability of oral iron protein succinylate: a systematic review of three decades of research

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ABSTRACT

Objective: Oral supplementation with iron is a standard intervention for treating or preventing iron deficiency with or without anemia. Over the last few decades, various forms of oral iron have been developed to improve treatment tolerability and iron bioavailability. In this review, we gathered research data regarding the use of iron protein succinylate since it was first marketed in the 1980s.

Methods: Electronic databases – PubMed and the Cochrane Library – were searched for studies published up to March 2019. Clinical or observational studies reporting data on the tolerability of oral iron protein succinylate were included. Results were statistically described to evaluate and compare the efficacy and safety of iron protein succinylate with the comparators under study.

Results: Iron protein succinylate was investigated in 54 studies: 38 randomized clinical trials and 16 observational studies, with a total of 8454 subjects. Of them, 8142 were included in the efficacy analysis: patients were divided into three population subtypes: general ($n = 1899$), gynecological/obstetric ($n = 5283$), and pediatric ($n = 960$). In total, 6450 patients received iron protein succinylate, experiencing a significant change in hemoglobin and ferritin in all populations. The change in all parameters was similar or higher with iron protein succinylate compared to other iron treatments evaluated. Overall, study groups receiving iron protein succinylate reported the lowest rate of adverse events.

Conclusions: Although all iron treatments analyzed are effective and safe, our results suggest that iron protein succinylate may be an excellent choice to treat iron deficiency and anemia due to its superior effectiveness and tolerability.

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Iron protein succinylate; iron deficiency; iron-deficiency anemia; oral iron efficacy; oral iron tolerability; oral iron replacement therapy

Introduction

Anemia caused by iron deficiency is a widespread nutritional disorder, with important consequences for human health[1]. Although the overall prevalence of anemia drops in middle- and high-income countries due to better access to adequate food, specific populations in these countries remain at high risk of iron deficiency. This is the case of pregnant[2,3] and menstruating women[4,5], particularly adolescents, in whom the onset of menstruation overlaps with a stage of rapid growth and increased iron requirements[6]. Iron-deficiency anemia causes lethargy, fatigue, irritability, and breathlessness. However, various authors have suggested that iron deficiency in the absence of anemia may impair exercise performance and affect muscle fatigue and work[4,7,8].

The traditional approach to the treatment of iron deficiency was based on supplementation with ferric or ferrous salts, being ferrous sulfate the most popular form. Although ferrous sulfate has proven effective to restore iron stores in patients with iron-deficiency anemia[9], gastrointestinal adverse effects (typically epigastric discomfort and nausea) may compromise treatment adherence in real-life practice[10]. These adverse effects can be attenuated by administering the iron supplement with meals, but absorption may be reduced by approximately 40% under these conditions[11].

In the last decades, various forms of oral iron have been developed to overcome the limitations of traditional iron salts. Among these alternatives, iron protein succinylate is a highly soluble complex of iron bound to succinylated milk proteins (in addition to intolerance/hypersensitivity to the excipients, the origin of the protein, particularly casein, makes the product unsuitable for people with hypersensitivity to milk proteins). One remarkable characteristic of iron protein succinylate is that the whole complex precipitates at pH < 4, allowing iron to pass through the stomach inside a protein shell and, therefore, avoiding direct contact with the gastric mucosa. Once the complex reaches the duodenum, it resolubilizes and is hydrolyzed by pancreatic enzymes, thus releasing iron molecules in the gut lumen[12–14]. This uptake pathway reduces the gastrointestinal adverse effects typically associated with iron supplementation. Since it was first marketed in 1988, various studies have investigated the tolerability and effectiveness of iron protein succinylate compared with other iron formulations.

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In this systematic review, we analyze all therapeutic outcomes reported over three decades of use of iron protein succinylate in both the research and routine practice settings.

Methods

Data sources and search strategy

Potentially relevant publications were retrieved from the PubMed and Cochrane Library databases from January to March 2019. Searches targeted studies investigating the outcome of treatments with iron protein succinylate, irrespective of the comparator and the patient profile. Therefore, the term "iron protein succinylate" was used, and no filters or limits regarding the time of publication, study design or language were established. Articles without full text available were excluded from the record. In addition to manuscripts retrieved from the databases, the medical department of the companies that marketed oral supplements with iron protein succinylate were contacted and asked for additional reports (gray literature) regarding this formulation.

Study selection and eligibility

All records resulting from the electronic search were screened for adequacy. After removing duplicates, all manuscripts with full text available were assessed for eligibility. Reviews were not included in the record; however, relevant publications cited in the review and not retrieved in the electronic search were considered for eligibility.

Eligible articles had to be written in English, Spanish or Italian (or any other language with a translation available). All participants of any age or gender with oral iron treatment indicated for iron deficiency, anemia or prophylaxis of anemia (in case of pregnancy) were considered, as well as all comparators, including ferrous sulfate, ferritin extractive, ferrimannitol ovalbumin, iron polystyrene sulfonate, ferric gluconate complex, iron polysaccharide complex, or placebo. Studies evaluating the efficacy of iron protein succinylate with concomitant treatments were also included, but the latter group of comparators was excluded from the efficacy results analysis to minimize bias in this regard.

Data extraction and analysis

All data were extracted and recorded in a database specifically designed for this review. Descriptive data included the number of patients (total and in each study arm), presentation of the iron protein succinylate and dose, the comparator and dose, target population, indication and treatment duration of the treatment, and study design. All measurements of variables that lacked information about the testing method and/or units were not considered for the analysis.

Treatment outcomes included change (baseline and final means) in hemoglobin (Hb), ferritin, adverse events (AEs), and if mentioned, gastrointestinal adverse events (GAEs) and whether AEs/GAEs were related with the treatment or not. To minimize the risk of bias, all analyses were weighted by the number of patients in each study and treatment.

Results were presented as the weighted average for baseline and final values of each outcome with their corresponding weighted variance. This assessment was performed for iron protein succinylate and each type of comparator: ferric and ferrous complexes. All efficacy measures were categorized into four populations. All-patient (i.e. all patients included in the efficacy analysis), general (i.e. a set of patients including, postoperative, patients with gastrointestinal pathologies, and older patients, among others), gynecologic/obstetric, and pediatric populations (each included patients from studies with their respective target population, Tables 1 and 2). All analyses were descriptive, and no hypothesis tests were performed.

Results

Selection and characteristics of selected studies

The search of the electronic databases yielded 140 records, of which 50 were duplicates and four were considered invalid for not reporting quantitative data on the use of iron protein succinylate. Of the 86 full-text articles considered for eligibility, 64 corresponded to clinical studies investigating the use of iron protein succinylate in a total of 6946 subjects. Of these, 54 reported efficacy and tolerability results and were, therefore, included in the analysis (Figure 1).

Of the 54 studies included in the analysis, 38 were randomized controlled trials, 32 of which compared the efficacy results of iron protein succinylate with other iron complexes[15–46] (Table 1). Six randomized controlled trials[47–52] and one observational study[53] compared iron protein succinylate of various presentations with or without other medications, and 15 studies[54–68] investigated the effectiveness of iron protein succinylate without a comparator (Table 2). Overall, the studies selected for the analysis included a total of 8454 subjects: 8142 were considered for the efficacy analysis and 8005 for the tolerability analysis. Of all the patients considered for the efficacy analysis, 6450 (79.21%) subjects received iron protein succinylate and 1692 (20.78%) were treated with other ferrous or ferric complexes as comparator groups. Ferrous complexes included ferrous sulfate and iron polystyrene sulfonate ($n = 1010$) and various ferric complexes ($n = 682$), including: ferritin extractive, ferrimannitol ovalbumin, and ferric gluconate.

Pooled efficacy results

Table 3 summarizes the weighted averages of baseline and final values of Hb and ferritin for all subjects treated either with iron protein succinylate or other iron complexes in the three selected populations and for all patients.

Overall, 8,142 patients were included for the efficacy analysis, with an iron treatment duration of 23–180 days. Treatment with iron protein succinylate achieved high efficacy results in the analysis including all patients. The pooled analysis of pre- and post-treatment Hb in patients receiving

Table 1. Studies investigating iron protein succinylate treatment efficacy vs. other iron complexes. Data included in the pooled efficacy analysis.

Study	Randomized/ blinding	*n* patients treated with IPS*	*n* total*	Comparator/s	Populations	Indication	IPS dose (mg/day)	Comparator/s dose (mg/day)	Duration (days)	Analysis
Bianchi, 1988	Yes/SB	15	30	Ferritin	Pediatric (2 months–12 years)	Iron deficiency anemia	40/80	40/80	30	E & S
Bracchitta, 1988	Yes/OL	20	40	Ferritin	Gynecologic/obstetric	Iron deficiency anemia	80	80	40	E & S
Cogo, 1988	Yes/SB	15	30	Ferritin	General	Iron deficiency	80	80	30	E & S
Danisi and Frontespezi, 1987	Yes/SB	16	31	Ferritin	General	Iron deficiency anemia	80	80	30	E & S
DeRenzo, 1987	Yes/SB	25	46	Ferritin	General	Iron deficiency anemia	80	80	60	E & S
DiSomma, 1988	Yes/OL	10	20	Ferritin	General	Iron deficiency anemia	80	80	30	E & S
Grossi, 1988	Yes/OL	20	40	Ferritin	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	80	80	60	E & S
Guerresi, 1987	Yes/SB	15	28	Ferritin	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	80	80	30	E & S
DiGiacomo, 1987	Yes/OL	10	30	Ferritin/ferrous Sulphate	General	Iron deficiency anemia	80	80/105	28	E & S
Bregani, 1990	Yes/SB	22	40	Ferrous sulphate	General	Iron deficiency anemia	80	105	60	E & S
Landucci, 1987	Yes/OL	20	40	Ferrous sulphate	General	Iron deficiency in blood donors	80	105	30	E & S
Liguori, 1993	Yes/DB	549	1095	Ferrous sulphate	General	Iron deficiency anemia	120	105	60	E & S
Najean, 1995	Yes/DB	86	174	Ferrous sulphate	Gynecologic/obstetric	Iron deficiency anemia	120	105	60	E & S
Pogliani, 1990	Yes/OL	41	54	Ferrous sulphate	General	Iron deficiency anemia	80/120	105	60	E & S
Veneroni, 1996	Yes/DB	20	40	Iron yeast protein	General	Iron deficiency anemia in postoperative patients	40	40	30	E & S
Ambrosini, 1988	Yes/SB	15	30	Ferric gluconate	General	Iron deficiency anemia in patients with gastrointestinal pathologies medically or surgically corrected	80	125	30	E & S
Careddu, 1989	Yes/SB	75	153	Ferric gluconate	Pediatric (6 months–14 years)	Iron deficiency anemia	40/80	40/80	40	E & S
Minqi	Yes/OL	60	160	Ferric gluconate	General	Iron deficiency anemia	80	125	60	E & S
Pedrazzoli, 1988	Yes/OL	20	40	Ferric gluconate	General	Iron deficiency anemia	80	125	60	E & S
Scremin, 1988	Yes/OL	15	30	Ferric gluconate	General	Iron deficiency anemia	80	125	30	E & S
Marcacci, 1989	Yes/OL	125	250	Ferrous sulphate/ferric gluconate	Gynecologic/obstetric	Iron deficiency anemia	80	100/80	40	E & S
Careddu, 1993	Yes/DB	256	502	Ferrous polystyrene sulfonate	Pediatric (<14 years)	Iron deficiency anemia	60/120	52.5/105	60	E & S
Poggi, 1987	Yes/OL	17	36	Ferrous polystyrene sulfonate	Pediatric (6 months–9 years)	Iron deficiency anemia	40/80	52.5	60	E & S
Minganti, 1995	Yes/SB	8	15	Ferrimannitol ovalbumin	Gynecologic/obstetric	Pregnancy prophylaxis of iron deficiency	80	80	28	E
Rayado, 1996	Yes/SB	175	347	Ferrimannitol ovalbumin	Gynecologic/obstetric	Pregnancy prophylaxis of iron deficiency	40	40	60	E & S
Haliotis, 1998	Yes/DB	50	100	Iron hydroxide polymaltose complex	Pediatric (12 months–9 years)	Iron deficiency	4 mg/kg	4 mg/kg	60	E & S
Xing, 2013	Yes/OL	30	60	Polysaccharide iron complex	Pediatric (<35 weeks gestation)	Iron deficiency anemia in premature infants	4 mg/kg	4 mg/kg	60	E

*All randomized controlled trials accounted for balanced groups.
Abbreviations. DB, double blind; E, effectivity; OL, open label; S, safety SB, single blind.

Table 2. Other studies investigating IPS effectiveness and/or safety. Only IPS treatment data from these studies are included in the pooled efficacy analysis.

Study	Randomized/ blinding	*n* patients treated with IPS	Comparator	Population	Indication	IPS dose (mg/day)	Comparator/s dose (mg/day)	Duration (days)	Analysis
Leocata, 1988	Yes/DB	10	Ferritin	Pediatric (<12 years)	Iron deficiency anemia	4 mg/kg	4 mg/kg	30	S
Pujol, 2002	Yes/OL	30	Ferrous sulphate	General	Iron deficiency anemia	80	210/105*	180	S
Sironi, 1987	Yes/OL	10	Ferrous sulphate	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	40	105/iron rich diet	30	S
DePetris, 1988	Yes/CO	24	Ferric gluconate	General	Iron deficiency anemia in patients with gastrointestinal pathologies medically or surgically corrected	100	100	1	S
Kim, 2009	Yes/OL	26	Iron sucrose (IV iron)**	Gynecologic/obstetric	Iron deficiency anemia	80	Variable dose	21	E & S
Piccoli, 1990	Yes/DB	14	Placebo	General	Iron deficiency anemia in chronic kidney disease patients	120		60	S
Bianchi, 1993	No/OL	50	IPS + H2 receptor antagonist	General	Iron deficiency anemia in patients with gastrointestinal pathologies	120	120	60	E & S
Duntas, 2000	Yes/OL	11	IPS + L-Thyroxine	Gynecologic/obstetric	Iron deficiency anemia and subclinical hypothyroidism	80	80	90	E & S
Juarez-Vazquez, 2002	Yes/DB	371	IPS + folic acid***	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	80	80	60	E & S
Abelli, 1984	Yes/OL	40	IPS****	Gynecologic/obstetric	Iron deficiency anemia	80	80	30	E & S
Mollica, 1984	Yes/DB	40	IPS****	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	80	80	40	E
Nicola, 1984	Yes/OL	20	IPS****	Pediatric (8 months–13 years)	Iron deficiency anemia	3 mg/kg	3 mg/kg	30	E & S
Gruppoltaliano, 1992	No/OL	81	Healthy control	General	Iron deficiency in older people	80	0	180	E & S
Duntas, 1999	No/SB	8	Healthy control	Gynecologic/obstetric	Iron deficiency anemia and subclinical hypothyroidism	80		90	E & S
Trojachanec	No/OL	40	none	Gynecologic/obstetric	Iron deficiency anemia	40–80		60	E
Bedarida, 1983	No/OL	12	none	General	Iron deficiency anemia in patients with gastroenteric pathologies	60		40	E & S
Belloni, 1983	No/OL	10	none	Pediatric (<1 years premature and/or underweight)	Iron deficiency anemia	6–8		40–43	E & S
Goisis, 1983	No/OL	41	none	Gynecologic/obstetric	Iron deficiency anemia	80		40	E & S
HayaPalazuelos, 2001	No/OL	671	none	Gynecologic/obstetric	Iron deficiency anemia	80		90	E & S
Larramendi, 2006	No/OL	1	none	Pediatric (4 years)	Iron deficiency				S
Manfredi, 1987	No/OL	80	none	General	Iron deficiency anemia	4 mg/kg; 40; 80		30	E & S
Moggi, 1984	No/OL	30	none	Pediatric (5 months–9 months)	Iron deficiency anemia	40/80		30	E & S
Popovska	No/OL	30	none	General	Iron deficiency anemia	?		56	E & S
Sallusto,1990	No/OL	2996	none	Gynecologic/obstetric	Iron deficiency anemia	80		50	E & S
Schettini, 1984	No/OL	19	none	Pediatric (3 months–15 years)	Iron deficiency anemia	2–7 mg/kg		75	E & S
Sifakis, 2005	No/OL	105	none	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	80		120	E & S
Tolino, 1989	No/OL	40	none	Gynecologic/obstetric	Iron deficiency anemia in pregnancy	80		60	E

*210 mg/day during the first month of treatment then a switch to 105 mg/day dose. **Only data for IPS-treated patients is included in the efficacy analysis. ***IPS + folinic acid treated patients were included in the efficacy analysis as folinic acid is routinely prescribed to pregnant women; ****other presentations of IPS.
Abbreviations. CO, cross-over design; DB, double blind; E, effectivity; OL, open label; S, safety; SB, single blind.

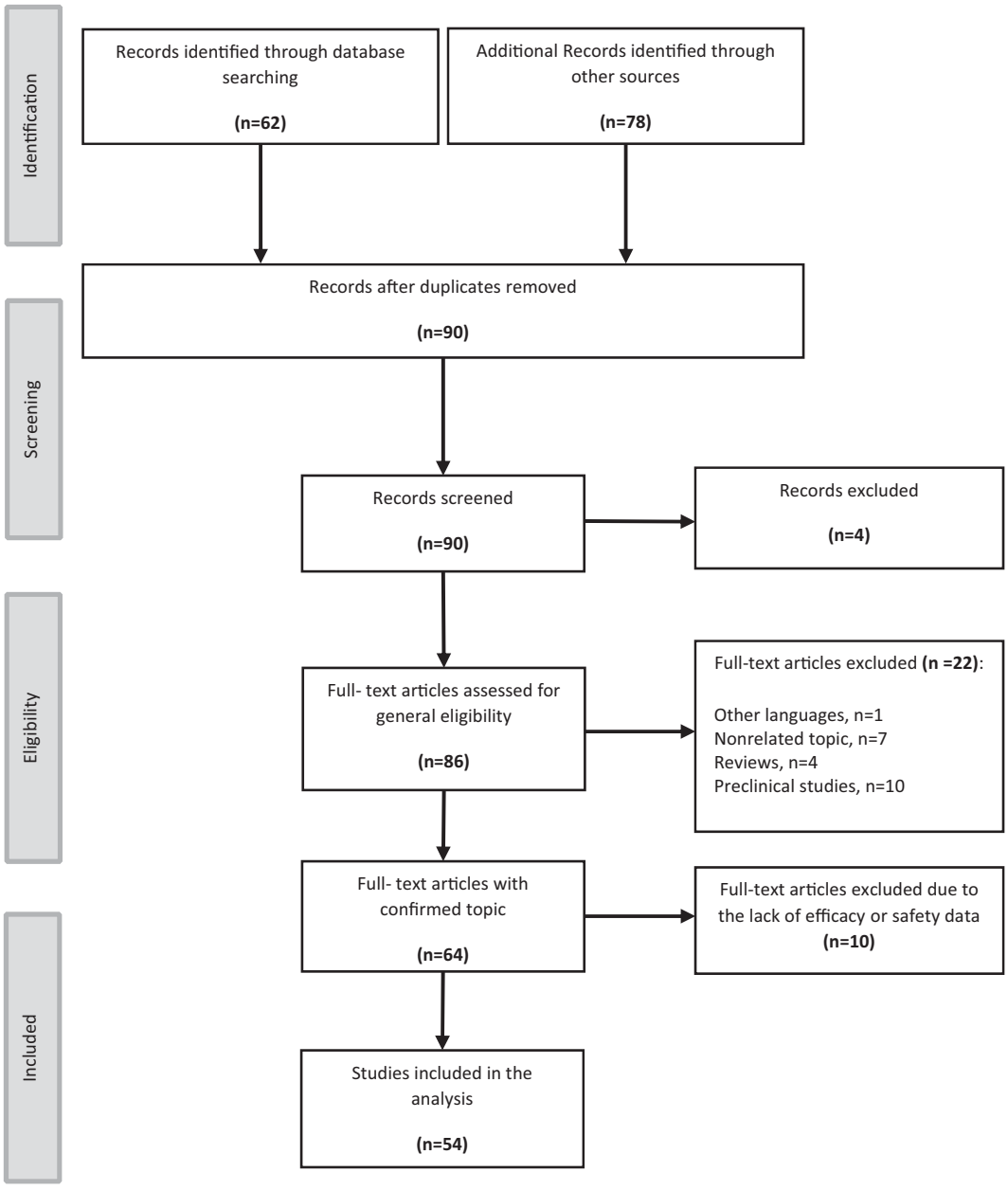

Figure 1. Flow chart of studies selected.

Table 3. Pooled efficacy results.

	N	Mean* Hb change (g/mL)				Mean* ferritin change (ng/mL)			
		Basal	SD	Final	SD	Basal	SD	Final	SD
All patients ($n = 8142$)									
Iron protein succinylate	6450	10.79 ($n = 6450$)	0.36	12.53 ($n = 6450$)	0.98	20.58 ($n = 3071$)	15.22	31.44 ($n = 3071$)	15.70
Ferrous complexes	1010	10.83 ($n = 1010$)	0.27	12.55 ($n = 607$)	0.28	21.14 ($n = 969$)	5.10	28.59 ($n = 969$)	4.28
Ferric complexes	682	10.66 ($n = 682$)	0.27	11.51 ($n = 682$)	0.22	18.10 ($n = 494$)	11.02	26.87 ($n = 494$)	15.28
General population ($n = 1899$)									
Iron protein succinylate	1091	10.59 ($n = 1091$)	0.44	12.69 ($n = 1091$)	0.65	22.58 ($n = 871$)	4.92	36.14 ($n = 871$)	6.47
Ferrous complexes (Ferrous sulfate)	607	10.99 ($n = 607$)	0.16	12.82 ($n = 607$)	0.15	22.96 ($n = 566$)	1.43	29.32 ($n = 566$)	1.30
Ferric complexes	201	9.20 ($n = 201$)	0.99	10.87 ($n = 201$)	1.45	27 ($n = 86$)	9.40	39.42 ($n = 86$)	14.55
Gynecologic/obstetric population ($n = 5283$)									
Iron protein succinylate	4838	10.71 ($n = 4838$)	1.56	12.39 ($n = 4838$)	1.25	21.45 ($n = 1763$)	19.76	31.06 ($n = 1763$)	21.74
Ferrous complexes (Ferrous sulfate)	138	10.10 ($n = 138$)	1.05	12.03 ($n = 138$)	1.23	31.55 ($n = 138$)	46.45	40.89 ($n = 138$)	36.84
Ferric complexes	307	9.59 ($n = 307$)	2.42	10.00 ($n = 308$)	2.54	17.93 ($n = 280$)	17.11	24.12 ($n = 280$)	20.04
Pediatric population ($n = 960$)									
Iron protein succinylate	522	10.84 ($n = 522$)	0.61	12.06 ($n = 522$)	0.52	13.10 ($n = 437$)	3.36	23.61 ($n = 437$)	4.53
Ferrous complexes (Ferrous polystyrene sulfonate)	265	10.79 ($n = 265$)	0.15	12.20 ($n = 265$)	0.13	11.83 ($n = 265$)	0.73	20.61 ($n = 265$)	1.69
Ferric complexes	173	11.06 ($n = 173$)	1.06	11.57 ($n = 173$)	0.84	12.48 ($n = 128$)	4.40	24.44 ($n = 128$)	7.78

*Weighted means.

Abbreviations. Fer, ferritin; Hb, hemoglobin; *N*, total number of patients; *n*, patients evaluated for a given endpoint or population; SD, standard deviation.

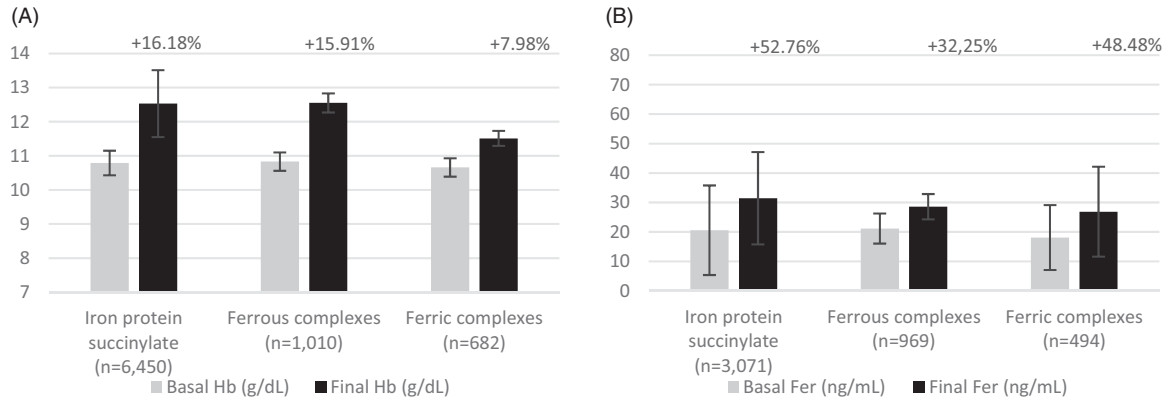

Figure 2. Pooled efficacy results for hemoglobin and ferritin in all patients included (A and B, respectively). Abbreviations. Hb, hemoglobin; Fer, ferritin. Labels indicate the weighted percentage of change for each endpoint in a given population.

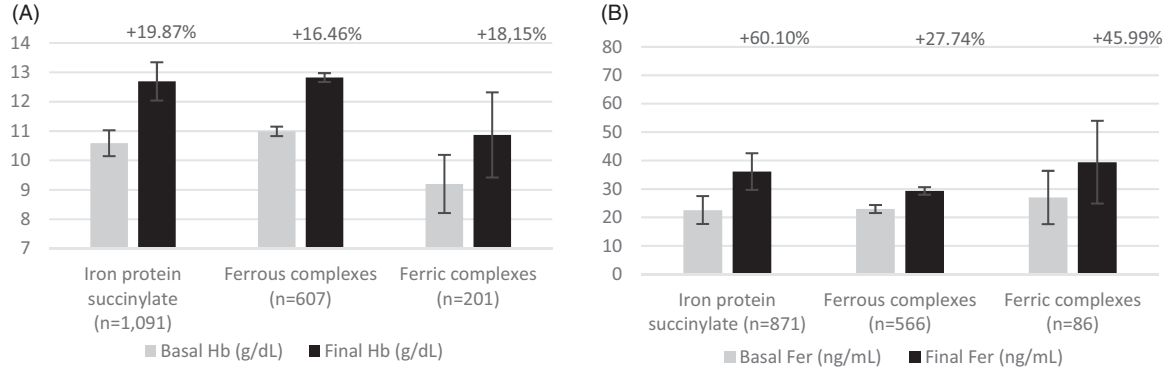

Figure 3. Pooled efficacy results for hemoglobin and ferritin in general population (A and B, respectively). Abbreviations. Hb, hemoglobin; Fer, ferritin. Labels indicate the weighted percentage of change for each endpoint in a given population.

protein succinylate, assessed in 6450 patients with a mean treatment duration of 49 days, showed a mean increase of 16.2% (+1.74 g/dl). This value was similar or higher than that observed with ferrous salts (15.9%, +1.72 g/dl; $n = 1010$; mean treatment duration of 58 days) and ferric salts/complexes (8.0%, +0.85 g/dl; $n = 682$; mean treatment duration of 49 days). The effect of protein succinylate on ferritin change, assessed in 3071 patients, showed a mean increase of 52.8% of this laboratory parameter. This increase was also higher than that observed with ferrous salts (35.3%, $n = 969$) and comparable or slightly higher than the one achieved with ferric salts/complexes (48.5%, $n = 494$) (Table 3, Figure 2).

The general population analyzed included 1899 subjects treated for 23–180 days. In this population, Hb change was the most frequently reported outcome. Overall, iron protein succinylate achieved positive results regarding change in Hb and ferritin with a mean treatment duration of 2 months. Patients included in the Hb analysis of iron protein succinylate (1091) showed a mean increase of 19.9% (+2.1 g/dl). This increase was comparable or slightly higher than that observed with ferrous salts (represented only by ferrous sulfate) (16.5%, +1.83 g/dl; $n = 607$) and ferric salts/complexes (18.2%, +1.67 g/dl; $n = 201$). Ferritin change in iron protein succinylate was assessed in 871 patients, who showed a mean increase of 60.1%. This increase was higher than that observed with ferrous salts (27.7%, $n = 566$) and ferric salts/complexes (46.0%, $n = 146$) as well. (Table 3, Figure 3).

The gynecologic/obstetric population analyzed included 5283 subjects, with a treatment duration of 28–120 days. In this population, iron supplementation was initiated as preventive treatment or as active treatment for iron-deficiency anemia either for pregnant women ($n = 362$) or gynecological population ($n = 4921$). Gynecologic/obstetric subjects treated with protein succinylate experienced a mean increase of 15.8% (+1.68 g/dl) in Hb levels ($n = 4838$; mean treatment duration of 45 days) and 44.8% in ferritin levels (assessed in 1763 patients). Mean increase in Hb associated with ferrous salts was 19% (+1.93 g/dl, $n = 138$) with a longer mean treatment duration (53 days), while for ferric salts the increase was smaller: 4.4% (+0.41 g/dl, $n = 307$; mean treatment duration of 52 days). Consistently with the trend observed in the all-patient population, the ferritin change associated with iron protein succinylate was higher than that observed in patients treated with ferric salts/complexes (34.5%, $n = 280$) and ferrous salts (29.6%, $n = 138$) (Table 3, Figure 4). Additionally, we evaluated the outcomes of iron protein succinylate treatment in studies that only included pregnant patients with anemia. The average trend of Hb increase was similar than for the overall gynecologic/obstetric population (16.9%, $n = 571$) with a mean (SD) baseline Hb of 10.3 (1.2) g/dl, but reaching a final mean (SD) Hb level of 12.1 (1.2) g/dl. Ferritin levels had

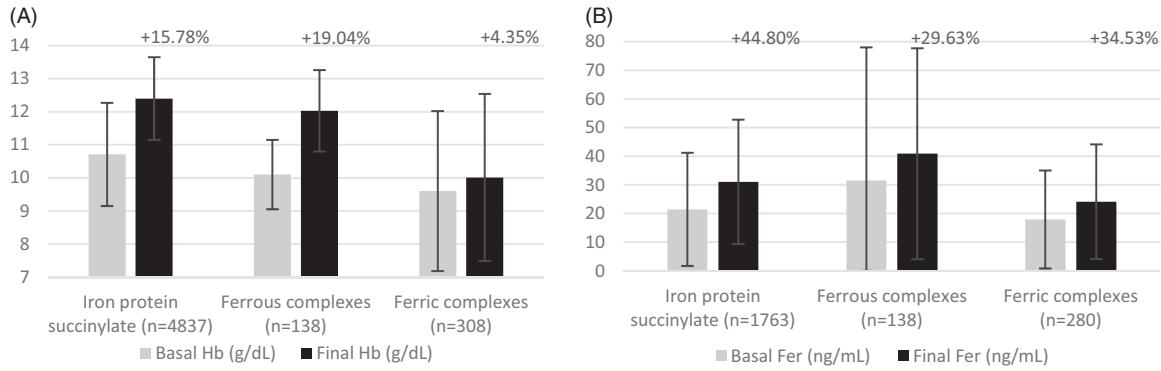

Figure 4. Pooled efficacy results for hemoglobin and ferritin in gynecological/obstetric population (A and B, respectively). Abbreviations. Hb, hemoglobin; Fer, ferritin. Labels indicate the weighted percentage of change for each endpoint. Labels indicate the weighted percentage of change for each endpoint in a given population.

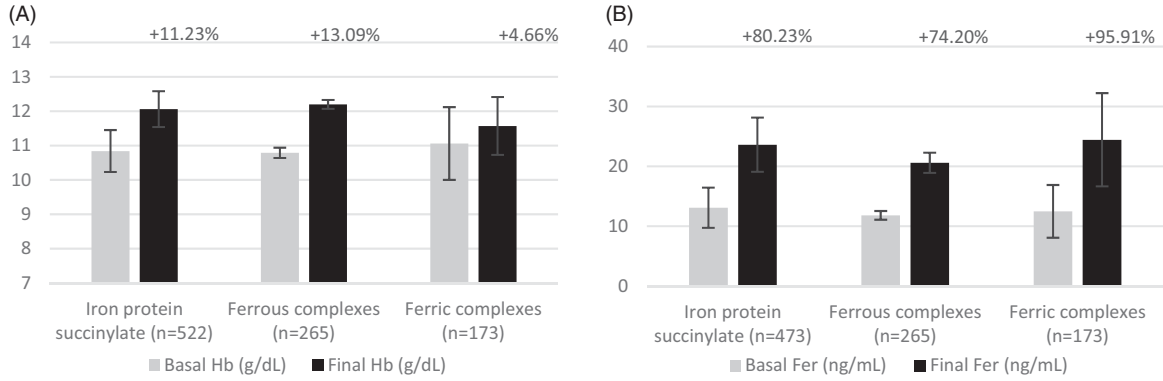

Figure 5. Pooled efficacy results for hemoglobin and ferritin in pediatric population (A and B, respectively). Abbreviations. Hb, hemoglobin; Fer, ferritin. Labels indicate the weighted percentage of change for each endpoint in a given population.

a lower increase in the pregnant anemic subpopulation than in the overall population or the rest of the gynecologic/obstetric population (23%, $n = 571$) after treatment with iron protein succinylate (mean [SD] baseline and final ferritin, 18 [22.5] and 22.1 [19.2] ng/ml, respectively).

The pediatric population included 960 subjects. Age ranged from premature infants to 14-year-old children, and treatment duration was from 30 to 60 days. Most subjects in this population were treated with iron protein succinylate and iron polystyrene sulphonate ferrous salt ($n = 522$ and $n = 265$, respectively), mostly at a weight-adjusted dose. In the pediatric population, the values for every outcome increased similarly for all treatments analyzed. Hb and ferritin changed from baseline after treatment with iron protein succinylate: 11.2% ($n = 522$) and 80.2% ($n = 437$), respectively (Table 3, Figure 5).

In addition to the populations categorized in Table 3 (i.e. all patients, general adult, gynecologic/obstetric, and pediatric), various studies assessed for efficacy included subjects with specific disorders or conditions. This was the case of 27 patients with gastroenteric pathologies that were medically or surgically managed, who received iron protein succinylate to treat iron-deficiency anemia[15,54]. Likewise, 35 patients included in the efficacy analysis had received iron protein succinylate in the surgery setting[15,44]. All these patients experienced a mean increase of Hb of 25% or more, reaching normal values of Hb after the therapy (i.e. >12 g/dl).

Additionally, the search of the electronic databases allowed the identification of two trials involving 30 patients with subclinical hypothyroidism who received iron protein succinylate: of these, 22 patients combined iron therapy with L-thyroxine[48,61]. All of these had a mean increase in Hb of 18.25%, reaching Hb normal values after treatment (i.e. >12 g/dl).

Finally, the analysis also included one trial involving 50 patients treated with iron protein succinylate while receiving H_2 antagonists as antiulcer therapy[53]. These patients normalized their hematologic parameters as expected, without clinical interactions between therapies. Mean Hb percentage change was 19.65%[53].

Pooled tolerability results

In this review, tolerability of all iron treatments reported was assessed in terms of adverse event rate per patient and whether this AE was gastrointestinal and/or related to the treatment, when this information was available. Forty-seven (87%) studies reported AE frequency, although only 32 (59.3%) provided information on the causality regarding iron supplementation.

A total of 924 adverse events were reported. Of these, 823 were gastrointestinal, and 438 were considered to be treatment-related. None of the AEs reported was serious. Iron protein succinylate was the formulation with the lowest adverse event rate, either related or non-related. Overall,

Table 4. Pooled safety data.

	N	Adverse events rate*	Gastrointestinal adverse events rate*	Related AE rate
Iron proteinsuccinylate	6187	0.08	0.07	0.04 ($n = 5320$)
Ferrous complexes	1130	0.25	0.23	0.26 ($n = 341$)
Ferric complexes	688	0.25	0.23	0.26 ($n = 516$)

*Average AE/GAE/relatedAE per patient.
Abbreviations. *N*, number of patients; *n*, number of patients evaluated for related AE.

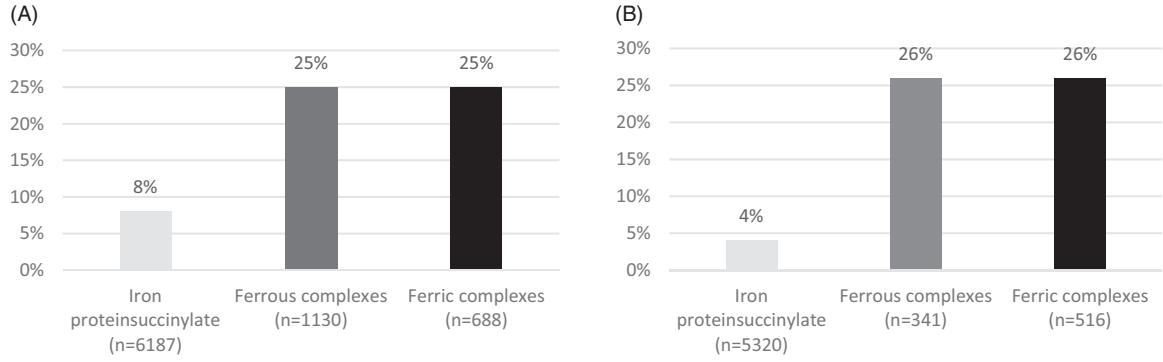

Figure 6. Pooled tolerability adverse events rate and related adverse events rate (A and B, respectively) for all patients included in the tolerability analysis. The "*n*" shows the sample size of each iron supplement in which AE rate and RAE rate has been calculate.

both ferrous and ferric complexes showed adverse event rates that were more than three times higher compared to iron protein succinylate (Table 4, Figure 6). Moreover, the relative AE rate of ferrous and ferric complexes vs. iron protein succinylate increased more than six fold when considering only treatment-related AEs (Table 4, Figure 6).

Studies investigating the tolerability of iron protein succinylate in pregnant women revealed a similar adverse event rate than that observed in the overall population (0.06, $n = 504$ vs. 0.07, $n = 6187$, respectively)[26,27,41,49,57]. In these patients, almost all reported AEs were GAE (GAE rate: 0.05, $n = 504$). None of the studies including patients who received iron protein succinylate in the surgery setting reported any AE[15,44]. Finally, the trial investigating the effect of combined treatment with iron protein succinylate and H_2 antagonists suggested a more favorable tolerability in patients receiving combined treatment than those receiving iron protein succinylate alone[53].

Discussion

In this systematic review, we provided pooled data on the efficacy and safety of iron protein succinylate from over 30 years of clinical experience and research with this formulation. The literature burden retrieved from this search amounted to 64 studies, in which nearly 7000 subjects received iron protein succinylate. As the purpose of the review was to provide a clinical perspective of iron supplementation, ten full-text articles reporting pharmacokinetic properties of iron protein succinylate were ruled out. Despite the heterogeneity regarding the methodological approach of these studies, they persistently reported that iron protein succinylate shows adequate bioavailability and good absorption[69]. Importantly, unlike other iron preparations, iron protein succinylate is well absorbed both under fasting conditions and after meals[70], which can potentially improve adherence to treatment.

Most clinical guidelines for the management of iron-deficiency anemia recommend unspecific oral iron supplementation to restore iron levels[71,72]. Even though all marketed formulations have proved to adequately do this, the low gastrointestinal tolerability of some treatments – such as those based on ferrous salts – may reduce the patient's adherence to treatment and, therefore, compromise its effectiveness[13]. Our review compared iron protein succinylate with other iron supplements, including widely prescribed ferrous salts, such as iron sulfate. The pooled efficacy analysis showed that iron protein succinylate was consistently associated with a significant change in Hb and ferritin, irrespective of the population. It is generally assumed that ferrous salts have a better bioavailability (due to a more efficient absorption) and as result, to be more efficacious than ferric complexes[73]. Our results suggest the same or superior efficacy results of iron protein succinylate treatment compared with the most commonly used oral ferrous salts. Additionally, iron protein succinylate treatment achieved these improved results in a 15.5% shorter mean treatment duration (49 vs. 58 days). Regardless, both iron protein succinylate and ferrous salts had better efficacy results than the ferric complexes analyzed. Importantly, differences between results of iron protein succinylate and other ferric complexes may be due to its unique formulation: iron protein succinylate precipitates at acid pH values, thus protecting the metal from gastric polymerization. The complex solubilizes at the duodenum, where the protein matrix is easily digested, and iron is absorbed[12]. Furthermore, it is well known that the co-administration of iron supplements and organic acids (i.e. ascorbic acid) enhance the absorption of iron, largely due to their ability to reduce ferric to ferrous iron[74]. Iron protein succinylate contains succinic acid, an organic acid that improves iron absorption up to 20–30%[75].

Compared to the general adult population in which the trend of higher change was maintained across analyzed outcomes, the pooled analysis in the gynecological/obstetric population yielded less, yet positive results. This attenuated trend may be partially explained by the heterogeneity of the populations included in each trial, which encompassed both pregnant women with diagnosed iron deficiency and healthy pregnant women for whom iron supplementation was prescribed as a preventive treatment for iron depletion. Concordantly, the evaluation of the percentage of change of Hb and ferritin in pregnant women with anemia compared with the general population results showed a weaker increasing trend, attributable to the different inclusion criteria between populations: various authors have observed that the effect of iron supplementation is likely to depend on changes in intestinal iron transport induced by iron deficiency and on the baseline iron status[76,77]. Therefore, any comparison between the outcomes of iron supplementation in healthy subjects and those with iron deficiency must be taken cautiously.

The pediatric population was the least represented and included mostly ferritin extractive and iron polystyrene sulfonate as comparators. Particularly in this case, all values increased similarly for all treatments analyzed. This population included very diverse subjects in terms of age and weight and, although doses were mainly weight-corrected, the heterogeneity of dosages included in the pooled efficacy analysis and the distinct requirements for different ages may have obscured true differences between treatments on the pooled results.

In the case of ferritin, the increase in hematologic parameters observed in all populations may seem scarce at first glance; however, it might be adequate considering the treatment duration of the included studies. Most guidelines recommend 3–6 months of iron treatment continuation once the Hb levels are restored to replete the iron stores and normalize ferritin level[78]. The average treatment duration with iron protein succinylate was of 49 days, clearly not enough to treat the anemia (notice that most of the patients were anemic) and recover iron stores. Nevertheless, it is noteworthy that with a shorter mean treatment duration (49 vs. 58 days), iron protein succinylate achieved better results than ferrous sulfate (average increase of 53 vs. 32%).

Overall, treatment with iron protein succinylate was associated with a much lower rate of AE than other iron formulations (assessed in 6187 patients). Ferrous and ferric complexes showed a similar AE rate, being more than threefold that of iron protein succinylate. Consistently, treatment with iron protein succinylate showed a good tolerability profile, not only in the global pooled safety analysis, but also in patients with special susceptibility such as those with gastrointestinal pathologies and pregnant women. Of all AE potentially associated with iron supplementation, gastrointestinal AEs are the most frequently reported and have been associated with poorer treatment adherence, particularly to ferrous sulfate[14].

Regarding related adverse events, even though most studies included in the analysis reported some tolerability results, the reduced number of related events and the poor analysis concerning their relationship with the iron treatment, as it is the case for studies including patients that received iron protein succinylate in the surgery setting, limits conclusions in this regard. Nevertheless, our results showed a better tolerability profile of iron protein succinylate-related adverse events compared with ferrous and ferric complexes, achieving a RAE rate five times lower.

The influence of non-absorbed oral iron on the balance of intestinal flora has been recently highlighted[79,80]. Although various authors have reported an association between iron supplementation and overgrowth of pathogenic species in children gut[81,82], the specific impact of iron protein succinylate on gut flora has not been assessed. Data presented in our review show that iron protein succinylate tends to cause less adverse events – including gut disturbances – than its comparators, thus suggesting a lesser impact on gut flora. Nevertheless, specific studies shall be conducted to further confirm the effect of iron protein succinylate on the intestinal flora.

Our analysis was limited by the unbalanced number of patients in different treatments and the heterogeneity of the investigated populations. Furthermore, a comparative analysis between preparations in patients with anemia or iron deficiency was not performed. However, rather than drawing strong conclusions regarding pairwise comparisons of iron treatments, our review was aimed at providing a picture of 30-year clinical experience and research with iron protein succinylate. In this regard, the exhaustive and barely limited search was likely to capture all this experience, albeit in a descriptive manner.

Conclusion

Three decades of research with iron protein succinylate have generated a considerable amount of evidence regarding its effectiveness and safety. Our pooled analysis of 54 studies indicates that iron protein succinylate achieved similar or higher efficacy results than other oral iron forms, including the widely used ferrous sulfate. Analyzed studies place iron protein succinylate as the iron complex with the lowest rate of AEs and GAEs, confirming its tolerability profile in the overall population and particular populations, such as pregnant women and patients undergoing surgery. Additional information provided in our review may help clinicians to make decisions regarding oral iron supplementation.

Transparency

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Declaration of financial/other relationships

AMF has no conflicts of interest to declare. JLMB is a full-time employee at ITF Research Pharma S.L.U. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors, AMF and JLMB contributed equally to the conception and design, the data acquisition, and the analysis of the results. All authors participated in drafting and critically revising the manuscript and gave the final approval to all the versions. Therefore, all authors agree to be accountable for all aspects of the work.

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