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Efficacy and Tolerability of Oral Iron Protein Succinylate in the Treatment of Iron Deficiency Anemia in Adults with Gastrointestinal Diseases

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Abstract: Iron deficiency anemia (IDA) is commonly associated with several pathological gastrointestinal (GI) conditions in adults, being induced through different mechanisms, such as chronic bleeding, chronic inflammation, malabsorption, autoimmune re-actions, or, quite frequently, as a combination of different mechanisms. All patients must be treated with iron supplementation with the aim of restoring normal hemoglobin levels and iron status. Oral iron compounds are the first line treatment options for ID clinical conditions, according to International Guidelines, as they have proven to be efficacious, safe, and relatively inexpensive. However, ferric salts are scarcely absorbed, and ferrous compounds present a poor GI tolerability. Iron-protein succinylate (IPS), an iron complex that keeps ferric iron bonded to the protein content of a succinylated casein shell at acid pH values, has been shown to release gradually iron into the intestinal lumen, protecting the gastrointestinal mucosa from eventual damage, an ensuring an optimal intestinal iron absorption. This review focuses on IPS in the treatment of IDA associated to a variety of GI medical conditions in adults. Results from diverse studies including IDA due to acute and chronic GI conditions, as well as IDA associated to gastric surgery, confirm a consistent improvement in hematologic parameters and clinical symptoms, and an optimal tolerability profile.

Keywords: Iron Deficiency, Iron Deficiency Anemia, Iron Protein Succinylate, Gastrointestinal Diseases

1. Introduction

Anemia is an increasing global health problem in low-, middle-, and high-income countries [1]. The most frequent single cause of anemia worldwide is iron deficiency (ID). Iron deficiency anemia (IDA) affects a considerable proportion of the adult and elderly populations [2]. Functional or absolute IDA is relatively common among adult patients attending primary care and internal medicine settings [3, 4].

According to the World Health Organization (WHO), in 2010 one third of the population worldwide, that is over 2 billion people, was anemic (defined anemia as serum hemoglobin (Hb) < 13 g/dL in males, < 12 g/dL in females, and < 11 g/dl in pregnancy) [5], and IDA accounted for nearly half of the whole anemia burden. Further-more, according to the Global Burden of Disease Study 2016, iron deficiency anemia is one of the five leading causes of years lived with disability burden and is the first cause in women [6].

Diagnosis and correct management of ID and IDA are critical because of the consequences of the disease on multiple organs and biologic processes, that can lead to organ dysfunctions and impair systems, such as central nervous system, cardiorespiratory system, immune response, vascular system, and urogenital and gastrointestinal tracts, with a negative impact on the health-related quality of life of those patients [5, 7, 8].

However, IDA is a rather frequently asymptomatic disease, or non-specific and vague symptoms may be present, like fatigue, asthenia, epigastric pain, and pallor. Hence, IDA may quite often go undiagnosed.

Iron deficiency (ID) and iron deficiency anemia (IDA) in gastrointestinal (GI) conditions

Iron deficiency anemia (IDA) is commonly associated with several pathological gastrointestinal (GI) conditions. GI diseases can induce anemia through different mechanisms:

chronic bleeding, chronic inflammation, malabsorption, autoimmune re-actions, or, quite frequently, as a combination of different mechanisms. Chronic blood loss from the GI tract (occult GI bleeding) is the most common cause of IDA in adult men and postmenopausal women [8]. Anemia is also the most frequent complication and extra-intestinal manifestation of the inflammatory bowel disease (IBD), as a result of multiple factors: chronic intestinal blood loss, mucosal inflammation and impaired dietary iron absorption play a significant role in its pathogenesis [9]. Likewise, ID and IDA following bariatric surgery may be developed as a consequence of intestinal bleeding, reduced iron absorption, decreased acid secretion from the stomach or elimination of the duodenum [10].

Even though the first step in the treatment of ID and IDA should be correcting the underlying cause to prevent any further iron loss, all patients must be treated with iron supplementation with the aim of restoring normal hemoglobin levels, red cell indices and iron status.

Ferrous sulphate or other better tolerated oral iron compounds are the first line treatment options according to International Guidelines [3, 4, 8, 11].

1.1. Iron protein Succinylate (IPS)

Iron-protein succinylate (IPS) is an iron complex containing 5% of iron engulfed in a succinylated casein shell. Succinyl casein is a protein carrier with a high content of electronegative residues which precipitates in an acid pH environment. Hence, succinyl casein is insoluble at pH values below 3.5, and becomes soluble at alkaline pH levels. It is present in a trivalent state (Fe^{3+}) in the form of a complex structure assembled into small polymeric clusters [12]. Unlike other iron salts, such as many ferric compounds, that are soluble at gastric low pH and release iron ions that can form insoluble and less absorbable complexes, IPS, thanks to its electronegative protein carrier, precipitates at acid pH values (2-4), keeping the iron tightly bonded to the protein, and producing highly soluble iron succinyl peptides later on by the digestive action of the intestinal proteases, that are able to release soluble Fe^{3+} [12, 13].

It has been shown that IPS can be administered after a meal, and its absorption is not affected by the gastric pH following food intake. No differences in the iron absorption from IPS complexes, under fasting and immediately-after-meal conditions, have been observed [14]. Additionally, no interaction between IPS and H2-receptor antagonists or antacids in patients affected with iron deficiency was shown, confirming that IPS can be absorbed independently of the gastric pH [15, 16].

The iron uptake occurs mainly in the duodenum and gradually decreases along the intestine (Figure 1). First, IPS is digested by proteases in the intestine, producing highly soluble iron succinyl peptides that are potentially able to release trivalent iron in a soluble form. Afterwards, the reduction of Fe^{3+} to Fe^{2+}, necessary for absorption through the divalent metal (ion) transporter 1 (DMT-1), is mediated by an iron reductase present in the intestine [13]. In addition, other mechanisms have been described to explain the absorption of those remaining IPS ferric compounds (with a higher molecular weight) that are not reduced to the soluble forms of divalent iron. They may enter the cell membrane by interaction with specialized proteins (mucins, β-integrins) that act as cofactors that would facilitate the iron complexes diffusion through the intestinal cell membrane, being then reduced after their cell internalization [13, 17]. By keeping iron bonded at acidic pH values, thus avoiding the release of high concentrations of iron ions that would damage the gastric mucosa, and by gradually releasing the iron to be intestinally absorbed, IPS results in a better GI tolerated compound compared with other iron salts [12, 13].

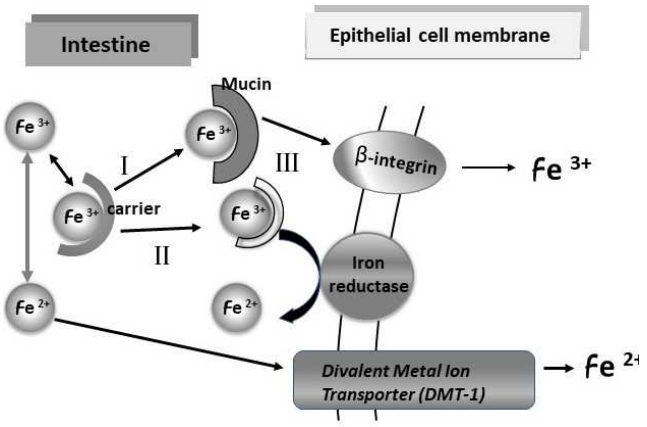

Figure 1. *Model for uptake of iron by the mucosa cell (adapted from Cremonesi P, et al. 2002).*

Clinical pharmacokinetics (PK) of IPS have been evaluated in two randomized studies. In a 4-hour PK study performed to assess iron absorption in ID patients, following 80 mg of IPS administration, a significant increase in serum iron was observed since 30 minutes after administration, and it was prolonged for a longer time than that of the comparator, ferritin [18]. These results were subsequently confirmed in another two PK trials: a first one comparing IPS with iron gluconate and placebo in a single dose cross-over randomized study, that included a sample of 24 non-iron deficient patients with diverse functional GI diseases [19], and a second one evaluating iron absorption and iron serum values in a group of anemic patients who had undergone gastrectomy at least one year before compared to a group of IDA patients of different etiology [20].

Oral iron protein succinylate has shown to be as effective as other iron therapies, such as ferrous sulphate, and to have a more favorable safety profile in gynecology, pediatric and non-gynecological adult population [21].

1.2. Objective

This paper is the first of a series of narrative reviews that will address the efficacy and safety profiles of iron-protein succinylate (IPS) for the treatment of ID and IDA in a wide range of clinical conditions presented in adults. In this publication the evidence of IPS in ID and IDA from gastrointestinal disease etiology will be reviewed.

2. Materials and Methods

For the purpose of the present narrative review, focused on the effect of IPS in ID and IDA due to GI pathologies and gastric surgery, ten studies have been selected and extracted from a previous literature search aimed at systematically reviewing the full evidence of IPS in diverse populations affected by several conditions over 30 years, and whose methodology and results have been already published [21].

3. Results

We selected ten studies (which included a total of 1,535 subjects) to evaluate the effect of IPS in ID and IDA due to both GI pathologies and gastric surgery [21]. Selected studies included 888 subjects treated with IPS –over 300 suffering from GI conditions–, 576 subjects treated with ferrous sulphate and 95 treated with ferric complexes. Table 1 summarizes the design, objectives, and main results of these studies.

Table 1. *Studies with oral IPS in iron deficiency associated to GI pathologies.*

Study	Design	Treatments	Duration	Population
Ambrosini	Randomized, controlled, single-blind trial	A- IPS 80 mg Fe^{3+}daily B- FG 125 mg Fe^{3+} daily	30 days	30 patients with ID due to GI conditions, corrected with surgery or drugs: 15, IPS; 15, FG
Bianchi	Prospective, parallel-group, open-label trial	A- IPS 120 mg Fe^{3+}daily B- IPS 120 mg Fe^{3+}daily + H2-A daily	60 days	100 patients with ID (GI pathologies in the IPS+H2-A group): 50, IPS; 50, IPS+H2-A
De Petris	Randomized cross-over controlled trial	A- IPS 100 mg Fe^{3+} B- FG 100 mg Fe^{3+} C- Placebo	Following 12 h fasting, blood samplings were conducted at 30', 60', 120', 180', 240', 300' and 360', after test dose administration	24 non-iron deficient male patients with malfunctional gastroenteric pathologies
De Renzo	Randomized, open-label trial	A- IPS 80 mg Fe^{3+}daily B- EF 80 mg Fe^{3+}daily	60 days	46 patients with IDA caused by chronic bleeding (11% with gastroenteric pathologies): 25, IPS; 21, EF
Liguori	Randomized, placebo-controlled, double-dummy, clinical trial	A- IPS 120 mg Fe^{3+}daily B- FS 105 mg Fe^{2+} daily	60 days	1,095 patients with ID or IDA (25.5% due to GI surgery or pathology): 549, IPS; 546, FS
Manfredi	Prospective, single-arm trial	IPS 80 mg Fe^{3+}daily	30 days	80 patients with IDA from diverse etiology (22.5% underwent GI surgery)
Popovska	Prospective, single-arm trial	IPS 40 – 80 mg Fe^{3+}daily	60 days	30 patients with IDA from diverse etiology (50% with chronic gastritis)
Pujol	Long-term, prospective, single-arm trial (comparison with a historical control)	A- IPS 80 mg Fe^{3+}daily for 6 months B- FS, 210 mg Fe^{2+}daily for the 1st month, followed by 105 mg Fe^{2+}daily for the next 5 months	180 days	30 patients with IDA (57% due to gastroenteric pathologies), treated with IPS; 30 patients with IDA (43% with GI diseases), treated with FS
Scremin	Randomized, open-label trial	A- IPS 80 mg Fe^{3+}daily B- FG 125 mg Fe^{3+} daily	30 days	30 patients with ID (17% with hemorrhagic gastritis): 15, IPS; 15, FG
Veneroni	Randomized. Double-blind, controlled trial	A- IPS, 40 mg Fe^{3+}daily B- iron protein derived from *saccharomyces cerevisiae* cultures, Fe 40 mg, daily	30 days	40 patients suffering from post-surgical ID: 20, IPS; 20, iron protein derived from *saccharomyces cerevisiae*

Table 1. *Continue.*

Study	Objectives	Efficacy Results	Safety Results
Ambrosini	1) Hematologic parameters 2) Clinical symptomatology due to ID 3) Tolerability	1) Both groups significantly increased the following parameters, after 1-month treatment: Hb, SI, HCT, MCV, MCH, MCHC. Results were more marked with IPS 2) Clinical symptomatology (asthenia, fatigue, and cutaneous-mucous paleness) improved in both groups, although more markedly with IPS	3) No adverse events were reported
Bianchi	1) Interaction of IPS with H2-A 2) Hematologic parameters. 3) Tolerability	1) No signs of possible interaction (negative or positive) were observed in the IPS + H2-A group 2) Both treatments achieved normalization of Hb and a significant improvement in Ferritin values	3) Clinical tolerability was good in both groups, although the IPS+H2-A group reported slightly better tolerability results
De Petris	1) PK assessment of: Serum iron levels increase, LIBC, TIBC 2) Tolerability	1) Significant increases in serum iron for both IPS and iron gluconate vs placebo. No differences between IPS and FG Decrease in saturated transferrin concentration (measured with LIBC) was observed in both IPS and FG	2) No adverse events were reported
De Renzo	1) Hematologic parameters 2) Tolerability	1) Faster and significant increases were observed in IPS vs EF in the following parameters: SI, Hb, HCT and MCV	2) Overall tolerability was good; no differences in adverse events between groups were reported
Liguori	1) Hematologic parameters 2) Clinical symptomatology due to ID and IDA (including an overall	1) At day 60, normalization of the main hematologic parameters was observed in both groups, albeit with greater values of Hb, HCT, Ferritin, and IS in the IPS group	3) A better tolerability profile was observed with IPS, with a significantly lower number of

Study	Objectives	Efficacy Results	Safety Results
	clinical rating) 3) Tolerability	2) Asthenia, fatigue, and skin and mucosal paleness significantly improved with IPS vs FS. Overall clinical rating was significantly in favor of IPS (78.9%) vs FS (67.6%)	reported adverse events; with shorter duration and later onset
Manfredi	1) Hematologic parameters 2) Tolerability	1) At study end, significant increases were observed in the following parameters: Hb, HCT, SI, RBC, MCHC, and TSAT Hematologic improvements were reported in the subgroup analysis	2) Overall tolerability was excellent according to the clinical judgement (adverse events were reported in 7.5% of the subjects)
Popovska	1) Anemic related symptoms 2) Hematologic parameters 3) Tolerability	1) Symptoms markedly improved after 15 days of supplementation 2) Significant improvement was observed in the parameters under evaluation: Hb, RBC, and erythrocytes' sedimentation	3) No adverse events were reported
Pujol	1) Hematologic parameters 2) Clinical symptomatology due to ID 3) Tolerability	1) Significant increases in Hb and Ferritin levels were observed in both groups at study completion, with no differences between them 2) Clinical improvement was reported in 86% of IPS and 80% of FS treated patients	3) Tolerability was good in both groups, but a higher number of GI adverse events was reported in the FS group (13% vs 3%)
Scremin	1) Hematologic parameters 2) Clinical symptomatology due to ID 3) Tolerability	1) Significant increases in IPS vs GF were observed in the following parameters: Hb, HCT, MCV, SI, and TSAT 2) Asthenia and cutaneous-mucous paleness were significantly improved in IPS vs GF	3) Few adverse events -and no difference between groups- were reported
Veneroni	1) Hematologic parameters 2) Clinical symptomatology due to ID 3) Tolerability	1) The following parameters were increased in both study groups: HB, RBC, HCT, SI, MCH, reticulocytes, and serum ferritin and transferrin. No differences between groups were observed 2) Clinical symptomatology was improved in both groups, with no differences between them	3) Overall reported tolerability was very good for all the patients

IPS: Iron Protein Succinylate; FG: Ferric gluconate; FS: Ferrous sulphate; H2A:; EF: Extractive Ferritin; ID: Iron Deficiency; IDA: Iron Deficiency Anemia; GI: Gastrointestinal; PK: Pharmacokinetic; LIBC: Latent iron binding capacity; TIBC: Total iron binding capacity; SI: Serum Iron; Hb: Hemoglobin; HCT: Hematocrit; RBC: Red Blood Cell Count; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; TSAT: Transferrin Serum Iron Saturation; H2-A: H2- receptor antagonist.

3.1. Oral Iron Protein Succinylate (IPS) in Iron Deficiency Anemia (IDA) Associated to Gastrointestinal (GI) Pathologies

Seven publications addressed the effect of IPS in adult patients with IDA due to several GI diseases. The spectrum of GI disorders included in those studies encompassed a wide range of medical conditions, like acute and chronic gastritis, duodenal and gastric ulcers, esophagitis, colon diverticulosis, intestinal polyps, hemorrhoids, and gastrointestinal surgery. In four of the studies, patients were randomly assigned to receive either IPS or an alternative oral iron treatment.

Iron absorption was tested in a single dose cross-over randomized study comparing IPS with iron gluconate and placebo in a population of 24 non-iron deficient patients recovered from functional GI pathologies. After the administration of a single dose equivalent to 100 mg of Fe^{3+}, the study showed a similar serum iron increase for both IPS and iron gluconate, proving the good bioavailability of IPS in humans [19].

Another randomized study compared IPS (80 mg Fe^{3+}/day) with iron gluconate (125 mg Fe^{3+}/day) in 30 patients with ID from different etiologies, including gastritis. Following 30 days of treatment, those patients in the IPS arm showed significantly better results in both hematologic parameters (Hb, Hematocrit (Hct), sideremia and TSAT) and symptomatology (asthenia and cutaneous-mucous paleness). Both drugs were well tolerated [22].

Forty-six patients suffering from IDA consequent to chronic bleeding (some with GI pathologies) were randomized to receive 80 mg of iron daily of either IPS or a comparator with an excellent tolerability profile, that is, an extractive ferritin (a micro-encapsulated and gastro-resistant formulation) in a two-month study. Most of the hematologic parameters (Hb, Hct, red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), serum iron, TSAT) were improved by both treatment groups at study completion, although changes were more marked in IPS patients. Reticulocyte count did not vary significantly in any of the study patients probably due to the gradual and slow renewal of the hypo-regenerative anemic status. Moreover, neither IPS nor ferritin significantly affect serum ferritin because iron re-serves are presumably only restored once anemia is cured. Both drugs showed a similar and acceptable tolerability profile [23].

The good efficacy and tolerability profile of IPS observed in the above studies was confirmed in a large randomized, double-blind, double-dummy, multicenter clinical trial, that was conducted to evaluate the efficacy and safety of 120 mg Fe^{3+}/day IPS compared with 105 mg Fe^{3+}/day ferrous sulphate (FS)[24]. One thousand and nine-ty-five patients with either ID or IDA, representative of the adult general anemic population, were enrolled, and followed-up for 60 days. Patients with esophageal varices, hemorrhoids, ulcerative colitis, intestinal polyps, and GI surgery were included. Hematology, haemato-chemistry, symptomatology, and safety were assessed.

At one month, a trend to the normalization of the main hematologic parameters in both groups was observed, including hemoglobin (Hb), Hematocrit (Hct), MCV and mean corpuscular hemoglobin concentration (MCHC). However, at study end, after 60 days, the values of Hb, Hct,

ferritin, and total body iron (Hb iron and storage iron) were greater in the IPS group, which may denote a more progressive and steady therapeutic effect. Additionally, some symptoms, such as asthenia, fatigue, and skin and mucosal paleness, significantly improved in the IPS treated population compared with the FS group [24].

The general tolerability, although favorable with both treatments, was significantly better with IPS; these patients referred a significant smaller number of adverse events (AEs), with a significantly shorter duration, and with a later onset. Importantly, GI side effects, namely heartburn, epigastric pain, constipation, abdominal pain, and nausea, were more frequently reported by the FS treated patients [24]. The more favorable GI safety profile with IPS may be explained by its chemical properties that favors its precipitation in the acidic stomach environment, protecting from the gastric mucosal damage, as well as by the gradual release into the intestinal lumen that, in turn, favors a better iron absorption [12, 13].

Three Further Studies Confirmed the Efficacy and Tolerability Characteristics of IPS in Patients Suffering from Different GI Conditions**.**

A prospective trial assessed the interaction of IPS (120 mg Fe^{3+}/day) with H2-receptor antagonists (H2-A) in 100 patients affected with IDA. Both study groups (IPS plus H2-A versus IPS alone), with 50 patients each, were comparable in baseline clinical and demographic characteristics, except for the presence of defined gastric diseases that were only present in the IPS plus H2-A group (50% with gastric ulcer; 36% with duodenal ulcer; and 14% with gastroduodenitis), and for the therapeutic options selected to treat these conditions. In addition, there was an expected significantly greater proportion of patients with ID without anemia in the IPS (70%) compared with the combined group (36%). Interestingly, the study showed no impact (neither positive nor negative) on the therapeutic efficacy, clinical tolerability, and biological safety, with the concomitant use of both drugs [15]. According to the authors, in spite of the increase in gastric pH subsequently to the H2-receptor antagonist therapy, IPS does not release its iron contents into the stomach mainly due to the protective protein shell, thus later allowing a sufficient IPS degradation and iron absorption at the proximal small intestine. A similar lack of interaction between IPS and antacids that permitted the concomitant administration of both drugs was observed in another study per-formed in pregnant women with IDA [16].

Another study compared 30 consecutive IDA patients who were treated for six months with IPS (80 mg Fe^{3+} daily) with a historical control of 30 FS treated IDA patients –FS group received higher doses: 210 mg Fe^{2+} daily for the 1st month, followed by 105 mg Fe^{2+} daily for the next 5 months–. Seventeen patients (56.6%) suffered from several GI diseases in the IPS group, while 13 (43.3%) had GI conditions in the FS group. There were no differences between both groups in hematological parameters (Hb, Ferritin) at study completion. However, GI side effects were reported in 3% of the IPS treated patients and in 13% of the historical group, those subjects who had received FS [25].

Finally, a prospective observational open-label study assessed 15 patients with chronic gastritis who suffered from IDA. Patients were treated with 40 to 80 mg of Fe^{3+} daily (IPS) and followed-up for 8 weeks. Improvement in both symptomatology and hematological parameters was observed at study completion. Furthermore, re-ported tolerability was notably good [26].

3.2. Oral Iron Protein Succinylate (IPS) in Iron Deficiency Anemia (IDA) Associated to Gastric Surgery

Three additional publications assessed the efficacy and safety profiles of IPS in adult subjects who developed IDA following gastric surgery interventions.

A randomized single-blind clinical trial compared the efficacy and safety of 80 mg of Fe^{3+}/day of IPS and 125 mg of Fe^{3+}/day of iron gluconate in 30 patients with ID due GI pathology following medical or surgical intervention for treating the anemia cause, for one month-period. Improvement in symptomatology and normalization of hematological parameters were observed with both drugs, but IPS proved to be more efficacious in ameliorating the clinical symptoms. No adverse events were reported in neither of the two study groups [27].

A second study prospectively assessed 18 patients who underwent different types of surgical interventions that caused IDA, from a cohort of 80 patients. Following 30 days of treatment with IPS (80 mg of iron per day), while all evaluated hematological parameter significantly improved, the increases in serum ferritin and serum iron concentration were notably marked, which reflects the good iron absorption profile of IPS. Treatment tolerability was optimal, with only 7.5% of the entire study population re-porting AEs [28].

Lastly, a third study randomized 40 patients suffering from post-surgical iron deficiency to 40 mg of Fe^{3+} daily of either IPS or a control group, consisting of a new iron protein derived from saccharomyces cerevisiae cultures in the presence of iron, and they were followed-up for 30 days. At study completion, both groups improved all the hematological parameters (Hb, Hct, RBC, MCH, reticulocytes, sideremia, ferritin, transferrin), and the reported tolerability was good for all the study patients [29].

Overall, it can be said that the efficacy and tolerability profiles of IPS is similar as or even better than the comparative controls in the population of patients with gastrointestinal pathologies and patients who underwent gastric surgery, and the results seem to be consistent throughout the different GI conditions.

4. Discussion

Oral iron is regarded by most of the international guidelines [30] and by the WHO [31] as the recommended therapy to treat or prevent non-complicated ID and IDA in the adult populations, and, also, the treatment mainstay for the absolute iron deficiency in those patients [32]. Oral iron supplements have for many decades proven to be efficacious, safe, and relatively inexpensive, to be selected as the preferred ID treatment option for many of the ID clinical conditions. There

is a broad variety of commercially available oral iron preparations, either as ferrous salts (sulphate, fumarate, gluconate, glycine-sulphate) or ferric compounds (protein-succinylate, ferrimannitol-ovalbumin, polymaltose complex).

However, oral iron supplementations, especially ferrous salts like ferrous sulphate, have been rather frequently associated with GI side effects, such as constipation, nausea, vomiting, diarrhea, and dyspepsia; and a high proportion of patients (between 30 and 70%) discontinue oral iron therapy because of those adverse events [33]. Furthermore, some oral iron supplements can exacerbate GI symptoms in patients with pre-existing GI inflammation, by contributing to further damaging the intestinal mucosa [34, 35].

IPS was developed to overcome the gastric and intestinal problems associated with the ferrous compounds and the low iron absorption frequently observed with many of the ferric iron preparations [12, 13]. By keeping iron bonded to its protein contents at low pH values, and by gradually releasing iron into the intestinal lumen, IPS protects the gastrointestinal mucosa from eventual damage, as well as it ensures an optimal and improved intestinal iron absorption [18, 20].

Across several studies conducted in a wide number of ID and IDA medical conditions suffered by the adult population, IPS treatment was associated with a consistent improvement in both hematologic parameters and clinical symptoms, and, in addition, with a remarkable safety and tolerability profile, as confirmed by the low incidence of GI side effects.

Among the hematologic parameters, the most consistently improved, independently of the study design and the selected comparator, were Hb, ferritin and serum iron concentration. These findings reflect the IPS associated increases in both functional iron and iron stores. Interestingly, these increases seemed to be fast, gradual, and steady, which is in accordance with the iron absorption rate tested in clinical pharmacologic and preclinical studies. Of note, all these hematologic improvements were also observed across the several populations enrolled in the above reviewed studies.

Recovery to normal hematologic values following IPS treatment in the IDA and ID populations was frequently observed, despite the short study duration in some of the commented trials between one and two months). Moreover, IDA clinical symptoms recovery was also commonly reported in most of the studies, comparing favorably with the reference drugs.

Overall, both IPS and its comparators in all the studies conducted in adults showed good safety and tolerability profiles. Nevertheless, differences favoring IPS were reported in several of the IPS versus FS studies [24, 36]. As expected from the known lack of GI mucosal damage with the use of IPS, patients treated with this medication, compared with those who received FS, reported less, milder, shorter, and later onset GI side effects [24]. The lower incidence of side effects in patients treated with IPS was shown even when higher doses of IPS were compared with lower doses of FS [24, 25]. This good IPS tolerability profile compared with other oral iron salts has been confirmed in a recently published systematic review [21].

The impact of non-absorbed oral iron on the gut microbiome, altering the microbial composition, with the result of a reduction in the beneficial intestinal flora and an increase in the replication and virulence of enteric pathogens, has been extensively discussed and documented in the medical literature [34, 37-41]. Ferrous compounds, like FS, have been shown to disturb the gut microbiota by promoting pathogenic bacteria growth, and frequently causing intestinal epithelial damage, inflammation, and infection [40, 41]. This shift toward an increase in the concentration of enteric pathogens inside the intestinal lumen has been confirmed in children with a high iron consumption [42] as well as in patients suffering from IBD [38, 43]. As explained before, IPS, due to its high solubility and consequent intestinal absorption, resulted in a better GI tolerability compared with the ferrous salts [12, 13], and an expected lesser impact on gut flora [21].

Another interesting clinical finding with IPS has been the lack of interaction with H2-receptors antagonists (H2-A). It is well known that H2-A and proton pump inhibitors (PPI), used for the treatment of peptic ulcer, result in clinically significant iron malabsorption due to gastric acid hyposecretion and the risk of achlorhydria [44, 45], which decreases the digestion of proteins and the absorption of vitamins and minerals. Long-term treatment with either PPI or H2-A has been associated with the development of IDA [46, 47]. A relevant clinical difference between classic oral iron supplementations and IPS lies in the absence of interaction (either positive or negative) during the concurrent treatment of IPS and H2-A [15]. As previously commented, IPS, due to its electronegative protein carrier that precipitates in an acid pH environment, engulfs iron in a succinylated casein shell, keeping it tightly bonded to the protein, and releases highly soluble iron succinyl peptides later on by the digestive action of the intestinal proteases [12, 13]. Likewise, IPS has not shown any interaction with antacids [16], another acid-modifying medications that have demonstrated to raise the stomach pH by neutralizing gastric acid, and consequently inhibited iron absorption and potentially contributed to ID and IDA development [48].

Interestingly, and related to the above studies, IPS capacity to remain insoluble within the stomach might also offer a competitive treatment advantage for bariatric surgery patients in whom the diminished hydrochloric acid secretion would hamper the reduction of ferric iron into the absorbable ferrous forms [49]. Moreover, as mentioned before, while the solubility of other iron compounds, like FS, decreases when gastric acid secretion is reduced (either by medication – PPIs, antacids or H2-A –, by infections – such as H. Pylori –, by nutrient deficiencies, or by bariatric surgery), which may hinder their absorption [50, 51], IPS doesn't need an acid pH to be highly soluble, since it has been shown to be better absorbed within a close to neutral pH [12, 13]. Clinically, IPS proved to be efficacious in improving hematological parameters in sub-jects who had undergone gastric surgery interventions [27-29]. Further specific studies should be conducted to confirm and evaluate the magnitude of its comparative benefit in treating IDA of bariatric surgery origin.

Some methodologic limitations regarding the selected studies must be acknowledged. Since most of the enrolled patients were followed-up for a short time (1 month), some of the study outcomes did not reach the statistical significance, albeit a constant trend was commonly observed. Furthermore, the number of patients was frequently rather small, and no sample size calculation was reported in the methods section of most of the respective publications. Another limitation is the high heterogeneity between the studies regarding the patients' characteristics. However, the great consistency in the efficacy (both clinical and hematologic) and tolerability results supports the validity of all the observations that have been commented in this narrative review.

5. Conclusion

Iron Protein Succinylate (IPS), unlike the ferrous salts (FS), keeps iron bonded to its protein contents at low pH values, and gradually releases iron into the intestinal lumen, thus protecting the gastrointestinal mucosa from possible damage, and ensuring an optimal intestinal iron absorption. IPS, compared with FS in several studies conducted in adults with either ID or IDA due to GI diseases, has shown a consistent improvement in hematologic parameters and clinical symptoms, reflecting an increase in both functional iron and iron stores. In addition, as expected from the lack of GI mucosal damage, IPS related GI side effects were milder, shorter, and with a later onset. Therefore, in light of the evidence derived from all the studies that evaluated the effect of IPS in the treatment of adult patients who suffered from either ID or IDA, whether of different gastric or GI etiology, or which coexisted with gastrointestinal pathologies, we can confirm that IPS compares favorably in efficacy and safety (especially, GI tolerability) with other currently available oral iron preparations.

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