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REVIEW ARTICLE

Are Iron Sucrose and Iron Sucrose Similar Equivalent? Analytical, Experimental and Clinical Determinations

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ABSTRACT

Iron Sucrose (IS) is a complex nanocolloidal intravenous suspension used in the treatment of iron deficiency anemia. Follow-on IS products, named Iron Sucrose Similars (ISSs) have obtained marketing authorization by the generic pathway, implying that identical copies of IS may be manufactured; this is the case in numerous countries. However many experimental studies and recent prospective and retrospective clinical studies showed major discrepancies in clinical outcomes, which might be related to differences in physicochemical properties. The aim of this work is divided in three parts: first to measure and compare physicochemical properties of IS and some ISSs available in the market using analytical procedures: size, size distribution, morphology and stability of these complex drugs revealed very significant differences between the products. Second, most experimental data suggest significant differences between IS and ISSs regarding oxidative stress and the inflammatory responses of liver, heart and kidneys in normal rats. Third, most clinical studies, coming from markets outside the United States have shown that these ISSs formulations may have safety and efficacy profiles that differ from the reference drug IS. As bioequivalence evaluation guidance evolves, clinicians should be educated on these potential clinical issues before a switch to the generic formulation is made in clinical setting.

Introduction

Iron is pivotal in a large number of physiological processes: Iron Deficiency (ID), and Iron Deficiency Anemia (IDA) are leading causes of disability [1,2], and common complications in a wide range of diseases such as Chronic Kidney Disease (CKD), inflammatory bowel disease and other gastrointestinal disorders, pregnancy/post-partum, heavy menstrual bleeding, cancer and chronic heart failure [3-8]. Several pharmaceutical approaches are possible for iron replacement: although well established, inexpensive and easily available, oral administration of various ferrous salts may be adequate in a large number of clinical situations, but shows limitations in effectiveness, tolerance, patient compliance and lengthy time required to replete iron stores [9]. When oral administration fails or is contraindicated to replenish body iron stores, intravenous (IV) administration of iron carbohydrate drugs is recommended [10].

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During the beginning of the last century, some parenteral preparations, followed by a high rate of side reactions, did not allow an extensive use of IV route with these generations of iron preparations [11]. In 1947, a substantial reduction in toxicity of parenteral iron was reported when the metal was chelated with saccharate moieties. Two years later, preparation and standardization of iron sucrose (IS) were elucidated [12]. Over the last 65 years, IS has been widely prescribed and became the most common IV iron treatment in most parts of the world including Europe, North America and Japan, due to its effectiveness and its proven synergy with Erythropoiesis Stimulating Agents (ESAs) in the treatment by IV iron of certain forms of IDA [13-15]. Moreover hypersensitivity reactions upon administration of IS are very rare [16].

Chemically, IS is a nanocolloïdal suspension composed of iron(III)-oxyhydroxyde nuclei containing not more than 20% of iron(II) stabilized by a saccharose shell via hydrogen bonds [17]. In recent years copies of IS, so called Iron Sucrose Similars (ISSs), have been approved via the generic approach despite the complex nature of this medicinal product [18]. Belonging to the pharmaceutical class of Non-Biological Complex Drugs (NBCDs), IS presents a high degree of complexity and unique characteristics not available neither to small molecules nor to biosimilars [19]. The manufacturing process is critical for the final attributes of the product and slight structural variations of the product might be related to potential side effects upon injections. In addition, such variations, may impact on the stability, and interact with the immune system, leading to changes in safety and pharmacokinetic/pharmacodynamics profiles.

In 2015 the European Medicine Agency released an updated reflection paper on the development of relevant assays to assess the characterization of IS as well as the evaluation and marketing authorization of ISSs [20]. Furthermore the US Food and Drug Administration decided in 2012 after discussions (personal communication) to prohibit for their market any ISS and declared in 2017 the evaluation of equivalence of iron colloids to be one of their regulatory scientific priorities [21].

This paper is devoted first to the analysis of the analytic methods for the physicochemical characterization of IS and ISSs. Attention is focused on size, size distribution and morphology of the nanoparticles, general stability of the colloidal suspensions and the evaluation of the fraction of labile iron in the samples. The second part compares the experimental experiences, non-clinical experimentations of IS and ISSs. Finally, the third part of this paper is dedicated to the clinical outcomes with IS and ISSs.

Analytic Comparison of IS and ISSs

The list of IS and ISSs products, investigatedby different laboratories, are summarized in Table 1.

Table 1: List of the products analyzed by analytic methods in different studies.

Sample (Brand Name)	Number of batchs analyzed	Supplier	Country	Short Name Used
Venofer®	6	ViforPharmaLTD	Switzerland	IS
Tian Xing	3	CDTTSZY	China	ISSs-CDTSZY
Wei X in Kang	3	Pude Pharma	China	ISSs-Pude Pharma
Sen Tie Neng	4	Hengsheng	China	ISSs-Hengsheng
IS-Claris	3	Claris Life Sciences LTD	India	ISSs Claris
IS-Azad	3	AZAD-Pharma	Switzerland	ISS-Azad

All the methods described were not utilized by all laboratories

The methods used for the analytic studies

1. The analytic methods used for IS and Chinese ISSs [22]:

- The Dynamic Light Scattering (DLS) determining hydrodynamic diameters of IS and ISSs; each result is the average of 3 sub runs constituted at least by 10 measurements
- The Gel Permeation Chromatography (GCC) was used to measure the molecularweight of IS and ISSs following the protocol previously published by Geisser et al [23].
- The quantification of labile iron. The amount of labile iron in IS and ISSs was evaluated using different

kits based on different chromogenic agents; chromazurolB assay, mak025 assay, and ferrozinc assay.

2. The analytic methods for the Indian ISS were [24]:

- Molecular weight determination: gel permeation chromatography instrument was utilized for the determination of the apparent molecular weight of iron sucrose formulations.
- Mass spectroscopy measures the mass of the molecules
- UV-Visible absorption spectroscopyis used to demonstrate the presence of octahedrally coordinated high spin Fe(III) ions.
- XRD analysis is made to observe the average particle size of the core of IS and ISS.

3. The analytic methods for the Switzerland ISS Azad were [25]:

- Molecular weight was determined by gel permeation chromatography using different equipment's.
- Atomic force microscopy
- In vitro analysis of kinetics of degradation
- Polarographic analysis

The Results from the Analytic Studies

1. The hydrodynamic diameters of IS and ISSs obtained by DLS measurements are reported on (Figure 1).

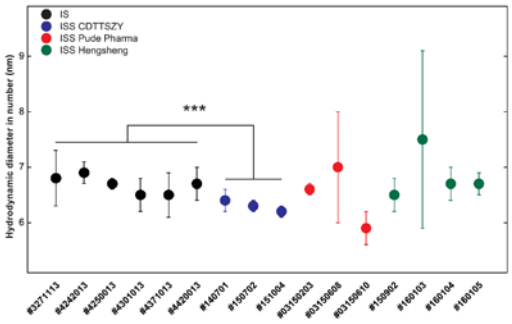

Figure 1: Hydrodynamic diameter in number of IS and ISSs CDTTSZY, pude pharma, and Hengsheng. Overall hydrodynamic diameter was <7nm. IS showed substantial intra-and interbatch robustness. All ISSs showed slight variation in size and higher interbatch variability. ISS CDTTSZY showed $p < 0.001$ to IS. Data reflect means of three measurements ±SD.

The size range of the nanoparticles varied between 5.9 and 7.O nm for the samples analyzed. Particles of ISS CDTTSZY showed significantly different size ($p<0.001$) when compared to IS. IS and ISS revealed a mono-nodal distribution with an average hydrodynamic diameter of less than 7nm. In contrast to ISSs, IS showed overall narrow size distribution and no significant intra- and inter-batch variability. For ISS a substantial inconsistency in size for the batches investigated was underlined. This phenomenon might be related to the lack in robustness of ISS manufacturing process.

2. The molecular weight determination. Using the United States Pharmacopeia Monograph [26] for iron sucrose injections, the weight average molecular weight (Mw)for IS is 34000-60000 DA while the number-average molecular weight (Mn) is not less than 24000 Da, and the Mw/mn ratio is not more than 1.7. All the results observed in different publications are reported in (Table 2).

Table 2: Results on gel permeation Chromatography for IS and ISS. Mw: molecular weight. Mn: Number-average molecular weight. Ratio Mw/Mn.

Sample	Reference	NbBatch analyzed	Mw Daltons	Mn Daltons	Mw/Mn
IS by TDF	22	6	43020±396	30966±2651	1.4
IS by Barot	24	6	58331±1544	37666±911	1.55
IS by Meier	25	10	34000-60000	24000	1.7
ISS CDTTSZY	22	3	41533±832	29066±450	1.4
ISS Pude Pharma	22	4	43900±1389	31266±3511	1.4
ISS Hengsheng	22	4	40750±914	29400±454	1.4
ISS-Claris	24	6	57744±1081	37235±2727	1.55
ISS-Azad	25	10	46318±1098	36400±1133	1.28

AllIS batches investigated by different teams showed a homogenous distribution of small bead-like which is in agreement with literature [17]. All ISSs samples from China showed the presence of heterogeneous mixtures. Size distribution for all ISSs was observed to be wider than for IS, including the Indian ISS, and the Switzerland

ISS. Moreover, extensive inter-batch differences were measured for ISSs samples with high variation in size, depending on the batch investigated.

3. The quantification of labile iron. The term labile iron identifies the fraction of iron in IS and ISS suspensions, which is only weakly bound to the iron(III)-oxyhydroxide core and potentially free to interact with the body leading to severe reactions [27,28]. The results of the quantification of labile iron varied in the range of 0.5 to13% depending on the assay used. There are three assays possible and all three assays revealed that ISS from Pude Pharma contained the lowest fraction of labile iron in comparison with IS and other ISSs. For the Swiss product no difference was found between IS and ISS Azad in the labile iron pool of both products [29]. The physicochemical characterization conducted reflects considerable dissimilarity in potential critical quality between IS and Chinese ISSs. The differences were less important with the Indian ISS and the Swiss ISS.

The Non Clinical Experimentations between IS and ISS

The methodology for the non-clinical experiments has been described essentially by the team of Toblli et al [30-33].

1. Animals and treatments

Three separate studies were performed, in which the investigators were blinded to the treatment groups. In all three studies, rats were housed in metabolic cages in a temperature controlled room. Injections were administrated at the same time every 7 days for 4 weeks. Due to the different concentrations of the studied iron compounds, they were diluted with saline in order to administer equal volume in each animal.

In study 1, non anemic Sprague-Dawley rats weighing 220-240g, were randomized with equal male-female distribution, to receive original IS and iron sucrose similar Fersucal [ISSFERSU] NPH China for Société Pharmaceutique Algerienne, or isotonic saline solution as a control. In study 2, same rats weighing 220-250, were randomized to receive original IS, or ISS Ferri [ISSFEINJ] from Emcure Pharmaceutical Pune India, or ISS Encifer (ISSENCI) from Encure Pharmaceutical , Pune India, or ISS IjzerhydroxydeSaccharose Complex (ISSIJZE) from Rafarm Pharmaceuticals Athens Greece, or ISSLikferr (ISSLIKFE)from Help S.A. Pharmaceuticals Athens Greece or isotonic saline solution as control. In study 3, same rats, weighing 250-275 g, were randomized to receive original IS or ISS Ferroven (ISSFEVEN)from Santa Farma ILAC Istambul Turkey, or ISS Fer MYLAN (ISSFEMY) from Mylan S.A.S, Saint Priest,France, or ISS Ferrovin (ISSFEVI) from RafarmPhamaceutical Athens, Greece, or ISS Fer Med (ISSFEMED) from MediceArzneimittelPütterGmbh, Iserlohn Germany , or isotonic saline solutions as a control.

The main research realized in each study were physicochemical analyses, blood pressure measurements, hemoglobin, serum iron, transferring saturation, liver enzymes, kidney parameters, light microscopy, immunohistochemistry, and histomorphometry.

2. The main experimental results

All IS lots complied with the USP specifications. Most of the ISS complied also with the USP specifications. Only ISSFEINJ, ISSENCI, ISSLIKFE, ISSFEMY, did not completely comply with the USP specifications. About blood pressure measurements, in all three studies significant decreases in systolic blood pressure and diastolic blood pressure were observed in ISS-treated animals throughout the treatment period compared to the animals treated with IS. Liver functions levels were significantly increased ($p < 0.01$) in all ISS groups compared with IS. Creatinine clearance was significantly reduced ($p<0.01$) in all ISS treated rats except in ISSFEMED, compared with IS and control groups. Proteinuria was significantly increased in all ISS-treated in rats compared to IS and control groups. Significantly higher ($p<0.01$) positive staining for iron (III) deposits were seen in the Kuppfer cells, sinusoidal epithelial cells, and hepatocytes of all ISS groups compared to the IS. In the heart, only low levels of ferritin staining were observed in animals treated with ISS, whereas IS treated animals displayed higher values for ferritin staining. In the kidneys, all the ISS groups displayed significantly ($p<0.01$) higher levels of iron(III) deposits in tubular epithelial cells compared with IS or control groups.

Observational Clinical Studies

Several ISSs appeared on the market at the beginning of the year 2009; this explains that the first published data about clinical efficacy and clinical safety were published only in 2011. There are six published studies, or case reports summarized on (Table 3).

1. Clinical study in nephrology (France) [34-37]

1.1. Period of the study: A long-term observational, non-interventional, single study was undertaken at the Centre Suzanne Levy, Diaverum group, Paris, France. The aim of the study was to compare anemia-related hematological parameters and anemia medication doses and costs in HD patients with iron deficiency anemia before and after conversion from IS to an ISS [34-37]. The decision to switch initially from IS to an ISS was made on the basis of economics (i.e, the ISS was significantly cheaper in relation to direct costs than the IS). Post observations of the increased iron needs, increased ESA needs and other medical concerns elected to switch back to the original IS. This longitudinal study hence describes the findings over a 30 months period divided into discrete equal periods to minimise bias due to seasonal fluctuations or other institutional practices.

The study compared five equal time periods of 26 weeks. Periods 1 to 3 were dedicated to demonstrate the haemoglobin (Hb) stability in an HD population receiving the original IS over an, 18 months-time (3 periods each of 26 weeks. All data in period 1-3 were retrospectively collected. Period 4 analyzed data after the switch to ISS. A small time period prior to data collection of period 4 was excluded as during this period both IS and ISS preparations were simultaneously available in the unit. Period 5, then analyzed patients after again switching back to IS. This prospectively observed period was initiated several months after the end of Period 4, to permit conversion of all patients back to IS (Figure 2).

During the full period of observation no other changes to medical management or clinical practices were implemented other than an adjustment of the Hb target (from 11.5-12 g/dL to 11-11.5 g/dL) level after publication of international recommendations suggesting a lower target Hb.

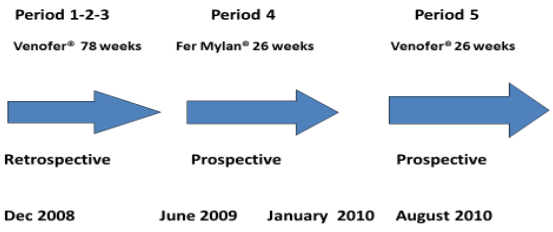

Figure 2: Design of the entire study: Period 1, 2, and 3 were retrospective in order to point the stability of the main parameters of HD patients under IS. Period 4 was the analysis after the switch from IS to ISS. After a few months, the return to IS was decided and the study was prospective.

1.2. Iron and erythropoiesis-stimulating agent (ESA) administrations: IS (Venofer®, Vifor International, St Gallen, Switzerland; 5 ml ampoules with 100 mg iron) or ISS (Fer Mylan®, ISSFEMY, Mylan SAS, Saint Priest, France, manufactured by Help SA Pharmaceuticals, Athens, Greece; 5 ml ampoules with 100 mg iron) were injected I.V. once a week at a dose of 25-100 mg iron, adapted to iron parameters, during periods 1 to 4. During period 5 after the publication of the synergistic effect of the administration of IV iron and ESA [43] during the same dialysis session, IV iron was injected every two weeks. Both I.V. iron preparations were diluted with saline solution (0.9%) up to 20 ml volume and infused over a one-hour period, between the second and the third hour of the dialysis session, in the arterial line before the dialyzer. The I.V. iron dose was titrated according to the most recent values of transferrin saturation (TSAT) and serum ferritin, targeting a TSAT level of 40-60% and a serum ferritin concentration of 500-800 µg/l.

The ESA darbepoeitin (Aranesp®, Amgen, Boulogne-Billancourt, France) was injected I.V. once every two weeks and titrated according to the previous 3-4 Hb values and taking into account any surgical or clinical event [44]. Medical management of the patients did not change during the study except for the switch from IS to ISS, and the switch back to IS.

1.3. Methodology: The study population comprised all HD patients who had undergone at least 350 dialysis

sessions in the unit during the study period and received at least one dose of I.V. iron. Measurements of Hb, serum calcium, serum phosphorus, (prior to dialysis) were obtained every two weeks. TSAT, serum ferritin, alkaline phosphatase, Parathyroid Hormone (PTH), 25-OH vitamin D, albumin, urea (before and after HD session), adequacy of dialysis (Kt/V), C-Reactive Protein (CRP), and total bilirubin were measured every three months. Routine data collection included demographics, primary cause of end-stage renal disease, number of dialysis sessions, and consumption of I.V. iron and darbepoeitin. All adverse events were reported according to applicable regulations and adverse events resulting in hospitalization were recorded.

dialysis sessions was 73±9 sessions per patient in Periods 1, 2, 3, 4 and 5. The mean number of Hb values recorded per patient was 64.2 (range 52-69), with a total number of 1008, 1023, 1068, 1012, and 1045 values obtained during Periods 1, 2, 3, 4,and 5 respectively.

Mean Hb concentration during Periods 1, 2 and 3, (IS administration), was 11.9±1.0, 11.8±1.0 and 11.8±0.9 g/dl, respectively. This decreased to 11.3±0.9 g/dl during Period 4 (ISS treatment) which was statistically significant ($p<0.0001$ versus Period 3).

Levels of serum ferritin and TSAT were stable during Periods 1-3 (Table 4). During Periods 3 and 4, the mean

Table 3: Summary of clinical studies comparing IS and different ISSs published in the literature.

Author	References	Formulations Studied	Study Design	Key Findings
Rottembourg J et al.	34-37	IS and ISS (Mylan SAS Saint Priest, France (ISS_{FEMY}) manufactured by Help.SA Pharmaceuticals, Athens, Greece.	Retrospective and prospective study pre and post switch in hemodialysis patients(n=75).	IV iron doses, ESA doses, and total drug costs increased and hemoglobin decreased post switch from IS to ISS and return to normal after the switch back from ISS to IS.
Martin-Malo A et al.	38	In vitro study of is and ISS, manufac-tured by Normon Laboratories Madrid, Spain	Determination of ROS production, ICAM-1expression and apoptosis in 8 patients.	ICAM-1 expression ROS and apoptosis higher with ISS than with IS.
Stein J et al.	39	ISS(Fer_{med}), MediceArzneimittelPütter GmbH & Co KG.	Case series of three patients receiving ISS who previously tolerated IS (300mg/300ml over 1.5 hour.	Adverse drug reactions, including urticaria, headache, and peripheral edema
Lee ES et al.	40	IS versus ISS_{FRX} (SejongPharmas, South Korea).	Retrospective study with IS and ISS in postpartum and gynecology.	Adverse events reported were significantly lower with IS.Injection site reactions and phlebitis significan- tly higher with ISS, especially with greater dilution.
Kuo KL et al.	41	IS versus ISS , Nan-Kuang Pharmaceutical	Stage 5 patients (n=40) receive ISS or IS.	CKD stage 5 patients with ISS had highest ROS production, ICAM-1 and VCAM-1
Aguera ML et al.	42	Switch from ISS_{NORM} (Madrid, Spain) to IS	Prospective study after institutional switch from ISS to IS.	Reduced IV iron and ESA doses required after switch. Hemoglobin remained stable

VCAM-1: Vascular Cell Adhesion Molecule; ICAM-1: Intracellular Adhesion Molecule; ROS: Reactive Oxygen Species.

1.4. Results: Sixty-six patients were eligible for inclusion in the analysis, the majority being male (68.2%). The mean age was 60±15 years and the mean duration of dialysis at the start of the analysis was 62±39 months. The primary causes of end-stage renal failure were diabetes (n=22, 33.3%), glomerulonephritis (n=15, 22.7%), hypertension (n=16, 24.2%) and other nephropathies (n=13, 19.7%). The mean number of

concentration of serum ferritin was 618±308 µg/l and 505±287 µg/l, respectively ($p=0.003$); mean corresponding values for TSAT were 45±7% and 24±10% ($p<0.0001$). After the switch back to IS serum ferritin increased back to the values observed during P1 to P3; more important is the return of TSAT to the values observed before the switch from IS to ISS.

Serum concentrations of phosphorus and calcium varied across the five study periods (Table 4). No significant differences across Periods 1-4 or between Period 3 and Period 4 were observed for PTH, albumin, or Kt/V. There was a significant increase between P1-P3 to P4 on 2 values, CRP and total bilirubin, indicating both the role of the oxidative stress due to the change from IS to ISS (Table 4), and a return to basal values after a switch-back to IS after a six months period on ISS. Most patients received IV iron therapy except seven (during Period 1), four (during Period 2), ten (during Period3), two (during Period 4) and five (during Period 5) respectively.

IV iron therapy was observed with values returning to the levels of Period 1-3 (51±28 mg/week).

The mean ESA dose per patient, stable from Period 1-3, also increased during Period 4 (from 0.52±0.50 µg/kg/week to 0.66±0.56 µg/kg/week) by 26.9% (p=0.005).

During the five treatment periods there were no adverse events and no hospitalization considered by the investigators to be related to the study drugs.

2. Study in Nephrology (Spain) [38,42]

The same team of Cordoba published two different papers [38,42]

The first paper was devoted to the effects of

Table 4: Hb levels, iron parameters and laboratory values in 66 hemodialysis patients during five consecutive periods of 26 weeks each. Patients received IS during Periods 1, 2, 3, and 5 and ISS during Period 4. Values are shown as mean (SD).

	Period 1 IS)	Period 2 IS)	Period 3 IS)	Period 4 ISS)	Period 5 (1S)	p value global[a])	p value (Period 1 to3 vs.4	p value Period 4 vs. Period 5[a])
Hb (g/dL) (SD)	11.9 (1.0)	11.8 (1.0)	11.8 (0.9)	11.3 (0.9)	11.8 (0.7)	0.001	<0.001	0.01
Serum ferritin (pglL) (SD)	621 (420)	644 (319)	618 (309)	505 (287)	649 (267)	0.004	0.003	0.04
TSAT (%) (SD)	43 (10)	43 (9)	45 (7)	24 (10)	41.5 (10.7)	<0.001	<0.001	<0.0001
Serum phosphorus (mg/dL)	5.4 (1.7)	5.3 (1.5)b	5.5 (1.6)	5.2 (1.2)	4.9 (1.1)	0.086	0.019	0.05
Serum calcium (mg/dL) (SD)	8.9 (0.6)	8.8 (0.6)	9.1 (0.6)c	9.0 (0.6)	9.1(0.5)	<0.0001	0.080	0.013
C-reactive protein (mg/L) (SD)	5.4 (4.4)	6.7 (9.4)	8.7 (14.2)	11.6 (16.0)	9.44 (14.6)	0.080	0.05	0.06
Albumin (glL) (SD)	40.8 (3.4)	40.1 (3.8)	39.8 (4.1)	38.4 (4.3)	39.6 (4.0)	0.45	0.08	0.08
Total bilirubin (mmol/L) (SD)	6.6 (2.0)	7.4 (1.8)	7.5 (2.0)	8.7 (2.3)	7.05 (2.1)	0.45	0.05	0.001
LDL-cholesterol (mmol/L) (SD)	2.0 (0.8)	2.1 (0.9)	2.0 (0.8)	2.1 (0.9)	1.9 (0.9)	0.45	0.37	0.06
KtN (SD)	1.45(0.19)	1.47(0.23)	1.47(0.25)	1.50(0.25)	1.48 (0.23)	0.45	0.19	0.19

ll between-period pair wise comparisons were non-significant unless stated otherwise Hb, hemoglobin; [a]ANOVA, [c]p=0.043 for period 2 versus 3, [c]p<0.001 for period 2 versus period 3

Figure 3 summarizes the mean doses of I.V. iron and ESA administered during the five treatment periods. Doses of both therapies were stable during IS treatment, with no significant differences between Periods 1, 2 and 3. Values for mean I.V. iron dose per patient increased significantly from Period 3 (56±33 mg/week) to Period 4 (67±32 mg/week), an increase of 21.1% (p=0.031). In Period 5, with the return to IS a significant decrease in

intravenous iron on mononuclear calls during the hemodialysis session [38], and a small part of this paper was devoted to the comparison of the injection of IS and ISSNORM in 8 hemodialysis patients studying the percentage of cells with Reactive Oxygen Species (ROS), Intracellular Adhesion Molecule (ICAM-1), and apoptosis. The percentage of cells with ROS production and ICAM-1 expression and apoptosis was significantly increased with ISS in comparison with IS.

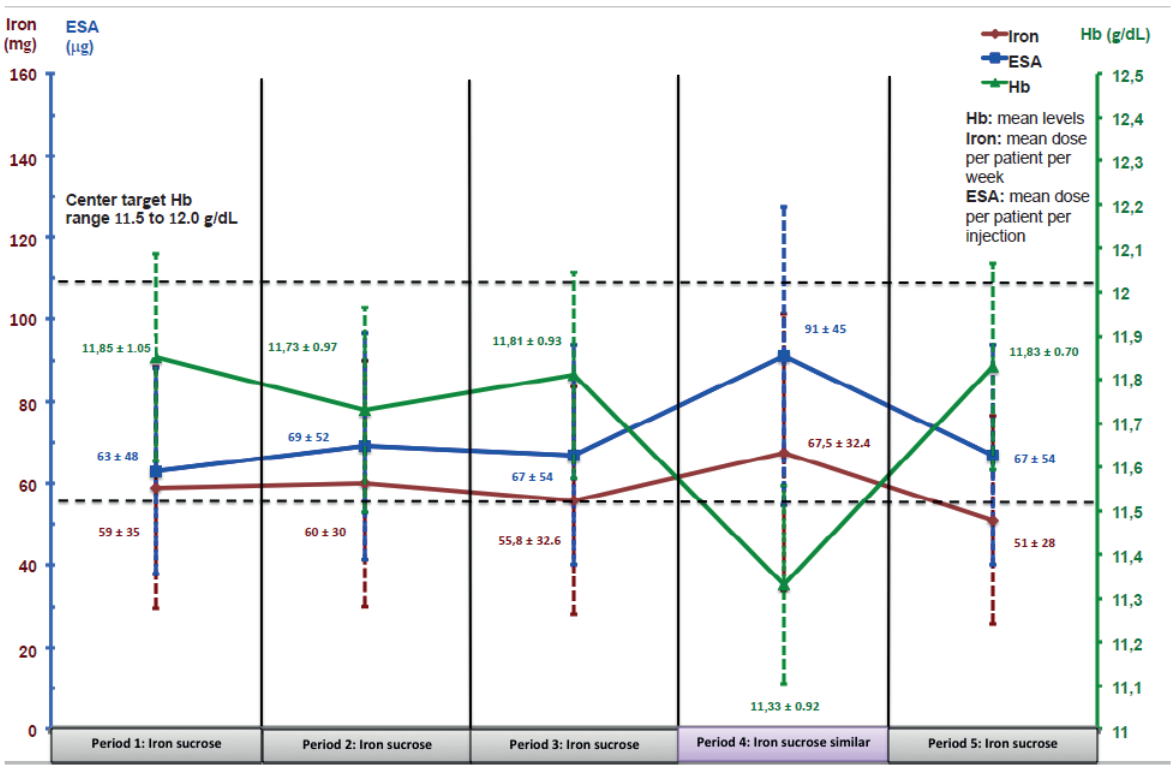

Figure 3: Mean Hemoglobin levels as well as IV iron and ESA before and after the switch from IS to ISS and same results after the switch back to IS.

The second study was a clinical study analyzing the effect of switching a high number of patients on hemodialysis from a ISSNORM back to IS, beginning in April 2011, where all patients were treated with the same ISS, modified in June 2012 back to IS for a 13 months period [42]. The study population was 342 subjects: 271 patients remained on dialysis during the entire periods, 55 patients died and 16 received a kidney transplant. There were no difference in the mortality rate between periods and no adverse events associated with the switch. The mean dose of iron per patient was 52.8±33.9 mg per week with ISS and 34.7±31.8 mg/week with IS ($p<0.001$) (Figure 4), representing a 34.3% decrease. The mean dose of ESA was 30.6±23.6 µg/week with ISS and 27±21 µg/week with IS ($p<0.001$) representing à 12.5% reduction. The hemoglobin level was stable throughout the study, around 11.6 g/dL.

3. Case report in gastroenterology (Germany) [39]

Three patients, presented in a german gastroenterology department in February 2011 with iron deficiency (TSAT< 20%) secondary to various gastroenterological diseases, should receive IS at a dose of 300mg in 300ml saline solution (in the same manner than the year before). Based on drug providers, the pharmacy switched the prescription to an ISS, without informing the prescribing physician. Within 1 hour of ISS infusion all three patients experienced adverse events such as urticaria, headache, hypovolemic dysregulation and peripheral edema. One patient experienced severe hypovolemic dysregulation, collapsed and was hospitalized for one day. The other patients experienced myalgia and were managed by symptomatic corticosteroid-based out-patient treatment. The events resolved without sequelae.

4. Study in postpartum and gynecology (South Korea) [40]

This Korean retrospective study was conducted at the inpatient obstetric and gynecologic department in order to study the safety of IV iron products. Patients received IV iron for correction of iron deficiency anemia immediately post-pregnancy or secondary to abnormal uterine bleeding or patients planned for having completed surgical interventions including myomectomy, hysterectomy, cystectomy and adnexectomy.

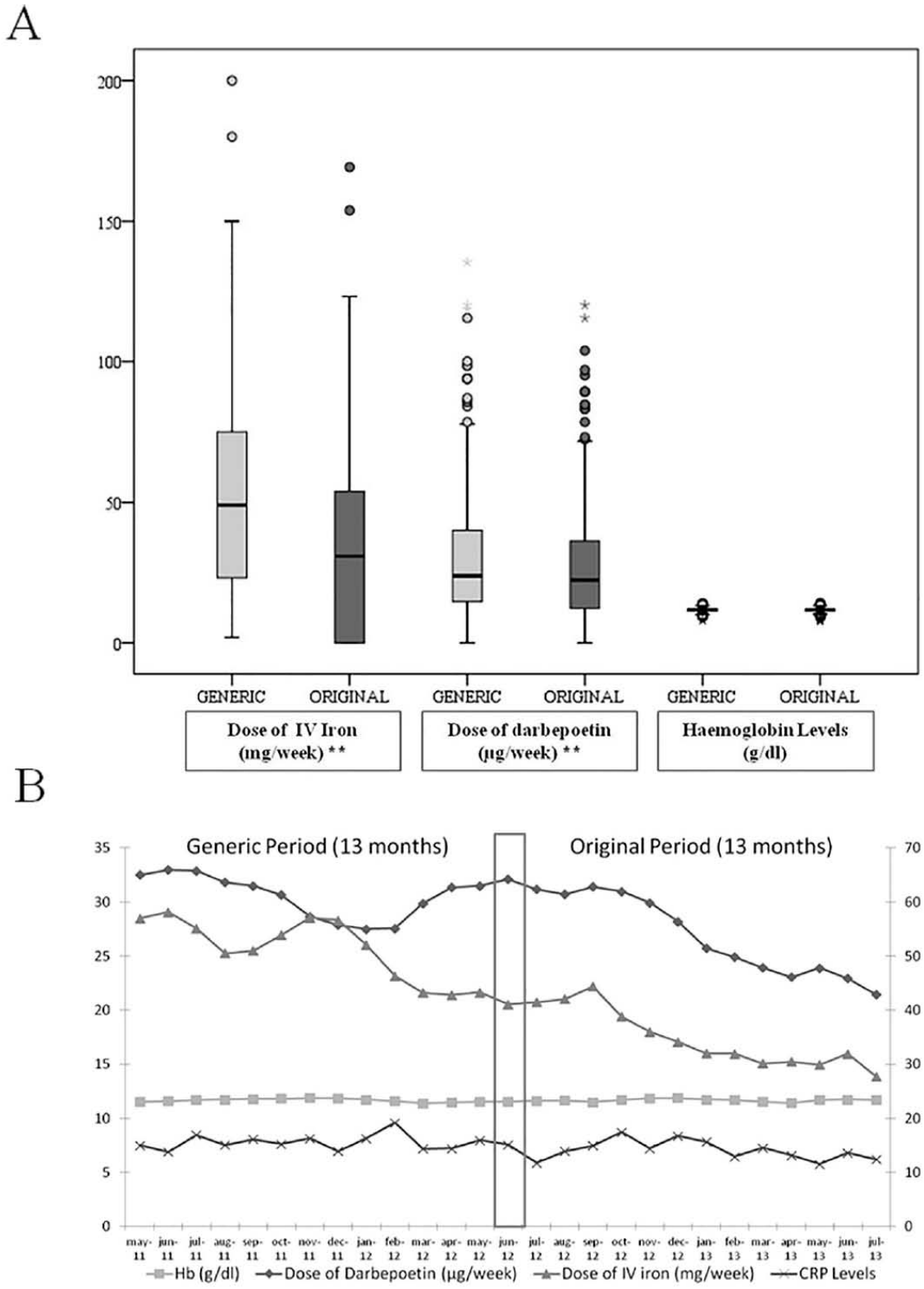

Figure 4: Hemoglobin Intravenous iron and darbepoetin alfa doses in each period: 4A per period, and 4B per month. From [42].

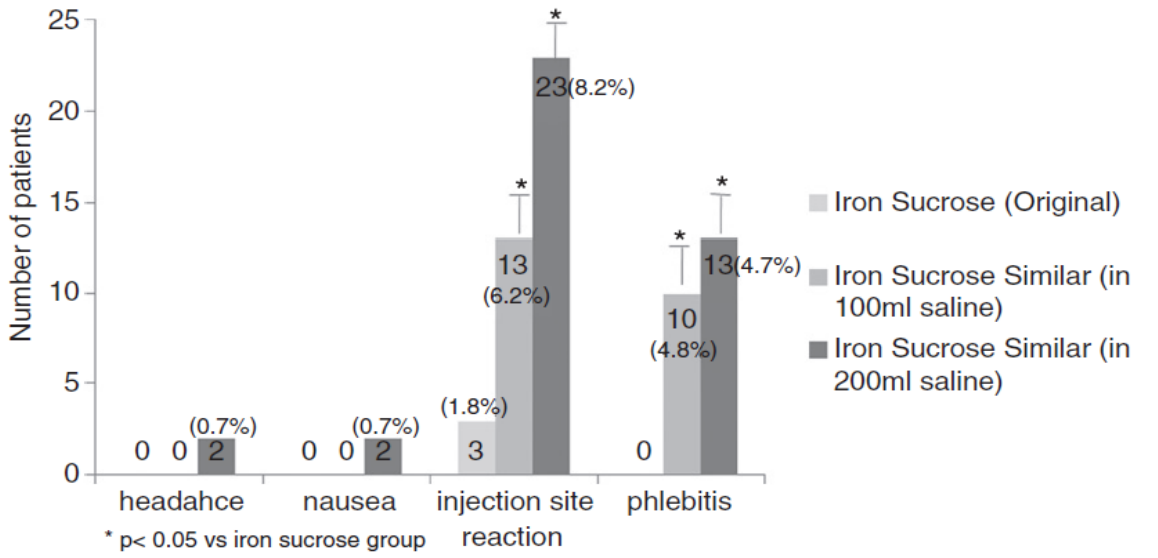

Figure 5: Adverse event profile of IS group, and ISS groups, in postpartum and gynecology. From [40].

Data were divided into two primary cohorts, IS and ISS; the patients assigned to ISS were assessed in two sub-groups based on the dilution volume. Group 1 (169 patients)received 2 ampoules of IS, each of 100 mg of iron, diluted in 100 ml of saline solution injected in 60 minutes. Group 2 (210 patients) received ISS administeredat a dosage of 200 mg, diluted in 100 ml of normal saline solution over approximately 60 minutes. Group 3 (279 patients) has the same ISS administration of 200 mg diluted in 200 ml over approximately 120 minutes.

In terms of safety, there were statistically fewer adverse drug reactions associated with IS compared with the ISS groups (1.8% for IS, vs 11% for ISS group 2, and 14.3% for ISS group 3). The most common events included injection site reactions and phlebitis ($p<0.02$) (Figure 5).

Discussion

This is the first paper about IS and ISS describing together the physicochemical characterization, the experimental data, and the efficacy and safety clinical parameters. The physicochemical characterization conducted reflects considerable dissimilarity in potential critical parameters between IS and some of the ISS studied. The analytic methods applied underlined the systematic presence of statistically significant differences in size, size distribution, morphology, stability and fraction of labile iron. IS is a colloidal suspension composed of spherical nanoparticles of less than 10 nmin diameter with slightly negative charge. The value for the fraction of labile iron varies depending on the specific assay chosen for its quantification but overall remains below 12%. Robustness of the assays was proven using IS as reference and comparable results were obtained with all the batches investigated by different authors [22-26]. Conversely, substantial intra- and inter-batch variability was evaluated for all the ISSs in each assay. Interestingly, it is noticed that differences between IS and one ISS might be visible in specific assay and absent in others. Moreover it is confirmed that molecular weight of each drug is in agreement with USP specifications for all samples tested. Inconsistency and insufficient homogeneity of ISS batches may indicate a lack of control of their manufacturing process, and partially by the absence of a clear definition of critical quality attributes. Most likely, ISS manufacturing process will be tailored to comply with specific future regulatory specifications of IS products. Some ISS such as ISSIZAD, and ISSCLARIS showed no difference with IS, but there are for these ISS no clinical data.

Findings from the animal experimentations may signpost long-term toxicity risks. The examination of hemodynamic, biochemical oxidative/nitrosative stress parameters in non clinical model demonstrated significant differences between all the ISS analyzed versus the IS group. IS, in contrast, exhibited a toxicity profile comparable to controls.

Anemia is a common comorbidity in various diseases such as Chronic Kidney Disease (CKD), inflammatory bowel disease and other gastrointestinal disorders, pregnancy/post-partum, heavy menstrual bleeding, cancer and chronic heart failure [3-8], resulting from reduced erythropoietin production by the impaired kidney and/or iron deficiency secondary to blood loss. Virtually all patients on dialysis require iron supplementation, and administration of an effective iron preparation is essential. Given the therapeutic importance of effectively controlling iron-deficiency anemia [45] and the risk of oxidative stress and hypersensitivity reactions [46] the I.V. iron therapy must be selected carefully, particularly since it is typically injected into patients with severe chronic disease over a long term.

Evidence from published clinical studies suggests that ISS preparations may not be equivalent to IS in either effectiveness or safety [34-42]. The clinical studies [34-37] also support these findings as the effectiveness of the ISS was inferior to the original IS. In other areas of medicine, concerns have also been expressed about the risks associated with switching to non-originator compounds in the absence of adequate clinical testing [47,48]. Because generic and original drugs must demonstrate bioequivalence, one would expect that switching formulations would not be associated with any significant change in everyday clinical practice [18,49].

In this population of stable hemodialysis patients, the switch to an ISS, was associated with a significant reduction in Hb level and reduced iron indices. This deterioration was observed despite an increase in both I.V. iron and ESA dosing, when adopting the ISS into clinical practices. On switching back to the original IS, the patients were stabilized and the dosing requirements where subsequently reduced for both the IV iron and the ESAs to levels observed pre-ISS use effectively demonstrating that the issue was indeed related to the ISS and not another external factor. This observational study made in France demonstrated the same results compared to the Spanish clinical study: 35% of increase of IV iron with ISS, and 13% of increase for ESA with ISS.

In this population of iron-deficient individuals, TSAT values decreased dramatically after the switch, indicating that less iron was available for erythropoiesis. This may signify that iron released from the ISS had been sequestered by other compartments of the body such as the liver, consistent with the more extensive iron deposits observed in liver tissues within the ISS groups of the experimental studies, published by Toblli [30-33]. The increased levels of liver enzymes recorded in the animal model were not mirrored by evidence of hepatic biological disorders in our dialysis population, perhaps because doses were far lower in the clinical study, but such an effect cannot be ruled out during long-term ISS therapy in dialysis patients. It has previously been observed that the administration of IV iron carbohydrate complexes with low stability, such as sodium ferric gluconate, can result in severe and extended parenchymal liver necrosis secondary to iron-induced lipid peroxidation in non-clinical models [50] and the high level of total bilirubin and low TSAT seen in the current clinical trial are consistent with some degree of hepatic toxicity and less stable molecular structures in the ISS preparations [30]. The significant increase in serum iron and TSAT described in the experimental study from Toblli [31,32], coupled with greater iron deposition, indicated more rapid release of iron compared to IS due to overloading of serum transport proteins. This finding might be attributed to the difference in the kinetics of iron dissociation after changes in the stability of the core of the iron-sucrose complex. Slight alterations in the manufacturing process of iron carbohydrates can result in disparities in the structure, molecular weight distribution and stability of the iron-oxyhydroxide core of the iron-sucrose complex [35].

Results

The results of the study using ISS (ISSFEMY)might be unable to be generalized to other IV ISS's formulations. Side effects in patient populations have also been observed with other ISS in gastroenterology [39], gynecology [40], and recently partly in nephrology with the changes induced after switching from a generic formulation to an original formulation [42]. Our recommendation is that the selection of a specific iron should not be based solely on financial considerations, between original molecules and their similar, assuming comparable efficacy and safety, because original and similar formulations might not be interchangeable.

The original reason for switching to an ISS was due to the financial aspect - namely that the ISS was cheaper than the IS. This complies with WHO guidelines which promote the use of generic drugs as a strategy to mitigate high pharmaceutical prices [49]. However, in the French and Spanish analysis, conversion to an ISS resulted in a substantial increase in the total cost of anemia medication (+27.3%). The increased overall cost was due to requirement for higher doses of both IV iron (+30.3%) and ESA therapy (+27.1%). As such the cost benefits of the cheaper direct drug costs are negated with the overall cost which then refutes the rationale for a switch based on financial perspectives.

Conclusion

The treatment of anemia in various diseases with the original IV iron–sucrose formulation permits lower doses of both iron and ESAs for anemia management when compared to an ISS, and in some other studies less adverse events. The original IS was more effective in achieving target iron and Hb levels with lower individual doses, representing both a cost saving (versus a similar formulation) and perhaps also a long term safety benefit (as unclear where the excess iron from the ISS is deposited). Switching from the original iron sucrose formulation to a similar formulation destabilizes this population and the return to the original formulation of iron-sucrose authorizes the restoration of adequate parameters.

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