IS IV IRON SUCROSE SIMILAR SAFE FOR MY PATIENTS?

Jeong Jae Lee, M.D., Ph.D.

Department of Obstetrics and Gynecology

Soonchunhyang University Hospital

Seoul, Korea

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Contents

Introduction

The role of intravenous (IV) iron for treatment of iron deficiency anemia (IDA) in obstetrics and gynecology

Is IV Iron Sucrose Similar (ISS) Safe for My Patients?

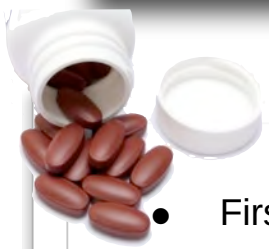
Clinical and non-clinical data suggest reduced efficacy and/or safety concerns with various ***ISS's***

Conclusion

ISS may affect stability of the iron complex, which can lead to difference in safety and efficacy

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Benefits of IV Iron Compare to Oral Iron



- First choice option for treatment
- May produce gastrointestinal disorders
- Limited by
  - poor absorption
  - low efficacy
  - poor compliance

- Rapidly deliver to the bone marrow
- Repletion of iron store is rapid
- High doses may be administered
- Frequency of adverse events is low

IV iron increased hemoglobin

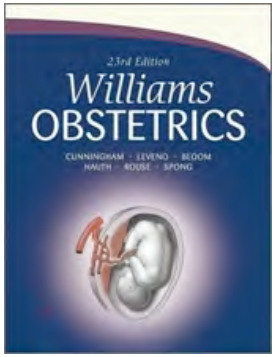
more rapidly, effectively, and convenient

than oral iron

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Obstetrics and Gynecology

- Blood business



OBSTETRICAL HEMORRHAGE: INTRODUCTION

Obstetrics is "bloody business." Although medical advances have dramatically reduce maternal mortality. Hemorrhage was a direct cause of more than 17 percent of 4200 Pregnancy Mortality Surveillance System of the Centers for Disease Control and Preve United Kingdom reported in the Confidential Enquiry into Maternal and Child Health (2 workers (2008) reported that 12 percent of maternal deaths were caused by obstetr for admission of pregnant women to intensive care units (Gilbert, 2003; Hazelgrove,

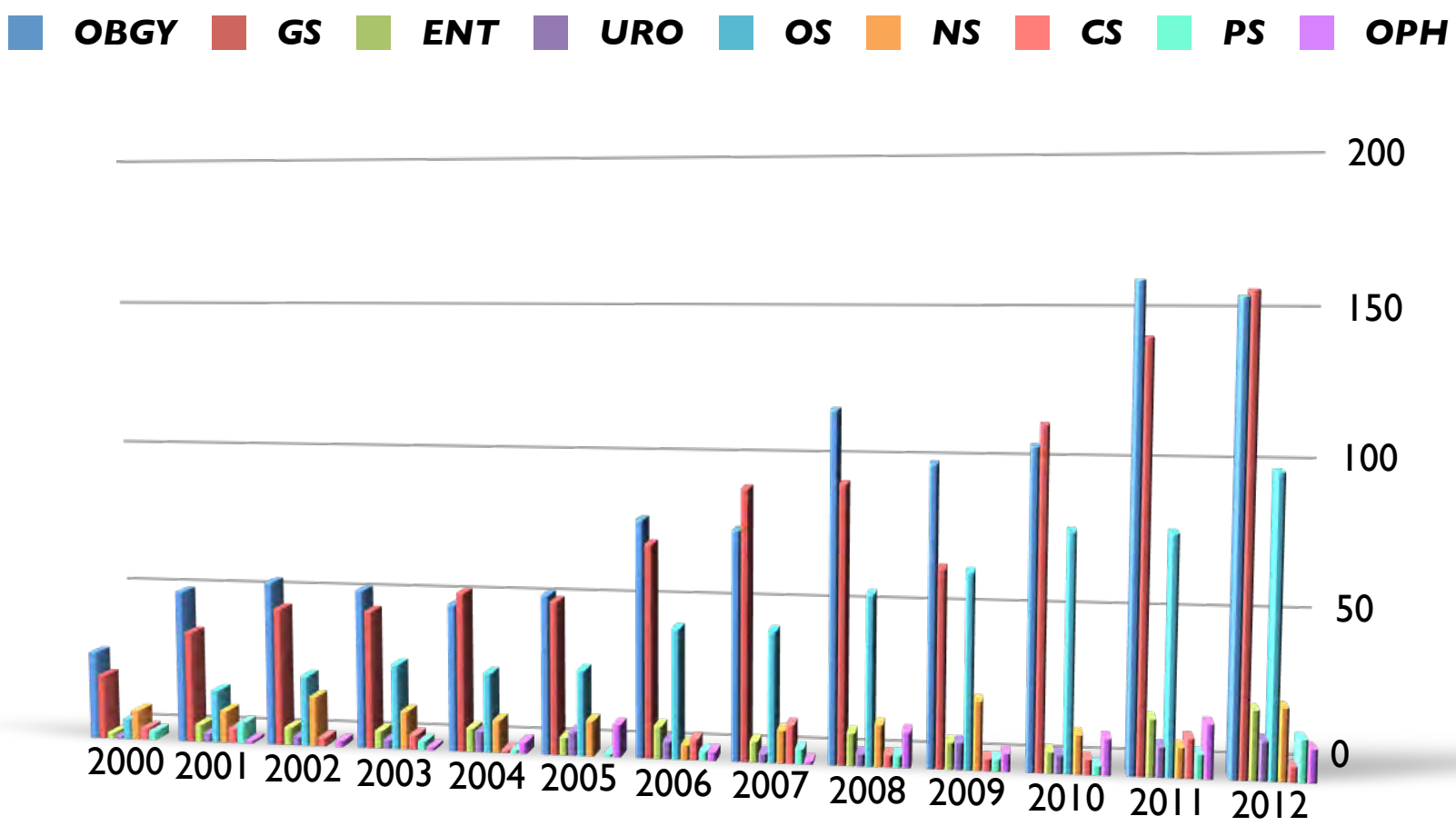
- Anemia

Diagnoses	Value
Menorrhagia	***65 (34.4%)***
GI Bleed, Bleeding Ulcer or Gastric Erosion	27 (14.3%)
Chronic Kidney Disease	24 (12.7%)
Pregnancy	***20 (10.6%)***
Angiodysplasia	20 (10.6%)
Gastric Bypass	14 (7.4%)
Crohn's Disease or Ulcerative Colitis	13 (6.9%)
Cancer	8 (4.2%)
AV Malformation	6 (3.2%)
Fibroids	***5 (2.6%)***
Multiple Surgeries	4 (2.1%)

- Auerbach M et al. Blood 2009;114(Suppl):1555

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Surgical Patients Number Registered in the Center for Bloodless Medicine & Surgery at SCH University Hospital, Seoul



SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Development of Iron Sucrose in Korea

Year	Component	Dose	Price	Brand Name	
1999	Ferric hydroxide sucrose complex ***Original***	540 mg/mL ***5 mL/ampoule*** ***(100 mg/ampoule)***	₩11,053 ($ 10.05) ₩8,842 ***($ 8.04)***	***Venoferrum®*** (JW Pharma, Vifor Pharma Ltd.)	
2007	Ferric hydroxide sucrose complex Generic	540 mg/mL 5 mL/ampoule (100 mg/ampoule)	₩ 7,516 ($ 6.83)	Annerum® (BMI Korea)	
	Ferric hydroxide sucrose complex ***Generic***	540 mg/mL (20 mg as iron) ***10 mL/ampoule*** ***(200 mg/ampoule)***	₩ 11,272 ***($ 10.25)***	***Ferex®*** (Samyang Genex Bio)	
	Ferric hydroxide sucrose complex Generic	540 mg/mL (20 mg as iron) 5 mL/ampoule	₩ 7,516 ($ 6.90)	Ferrowel® (Hanwha Pharma Co.Ltd.)	

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Development of Iron Sucrose in Korea

Year		Dose	Price	Brand Name	
1999	Fer sucr	540 mg/mL ***5 mL/ampoule*** ***(100 mg/ampoule)***	~~₩11,053~~ ($ 10.05) ~~₩8,842~~ ***($ 8.04)***	***Venoferrum®*** (JW Pharma.)	
2007		540 mg/mL 5 mL/ampoule (100 mg/ampoule)	~~₩~~ 7,516 ($ 6.83)	Annerum® (BMI Korea)	
	Ferric hydroxide sucrose complex **Generic**	540 mg/mL (20 mg as iron) ***10 mL/ampoule*** ***(200 mg/ampoule)***	~~₩~~ 11,272 ***($ 10.25)***	***Ferex®*** (Samyang Genex Bio)	
	Ferric hydroxide sucrose complex Generic	540 mg/mL (20 mg as iron) 5 mL/ampoule	~~₩~~ 7,516 ($ 6.90)	Ferrowel® (Hanwha Pharma Co.Ltd.)	

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

IV Iron Treatment in IDA Patients at SCH University Hospital

April, 2000

2008

+

2008

2010

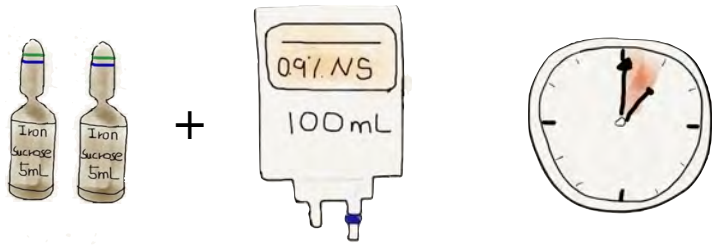
+

Adjustment of dilution
and administration time
(per manufacturer recommendation)

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

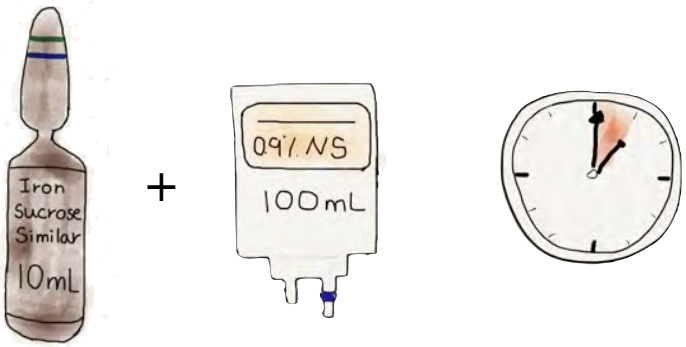
IV Iron Treatment in IDA Patients at SCH University Hospital

April, 2000



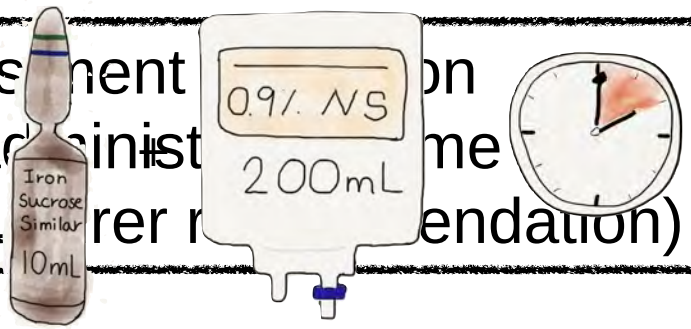
2008

2008



2010

Jan. 2011 Adjustment of administration time and administration rate (per manufacturer recommendation)



SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

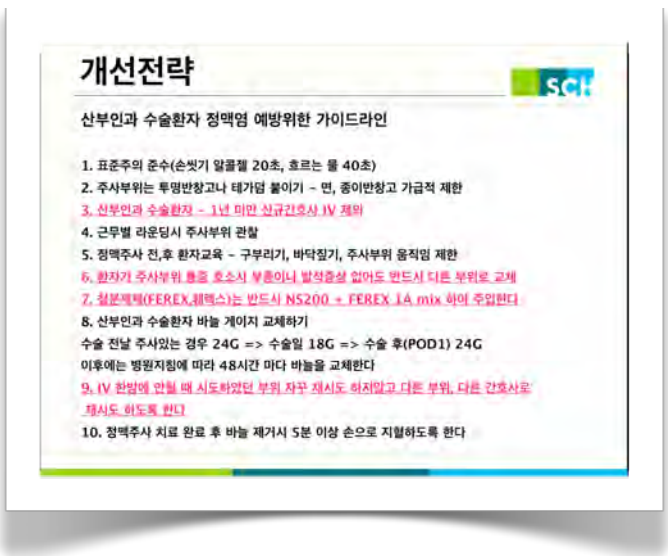
Adverse Events

- Continued – seemingly increasing in frequency

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Adverse Events

- Continued – seemingly increasing in frequency



- ***ISS discontinued at our site***
- Retrospective analysis to examine the true number of adverse events

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Is Iron Sucrose Similar Safe for My Patients?

Korean Journal of Obstetrics and Gynecology
Vol. 49 No. 1 January 2006

산부인과적 수술로 인한 빈혈교정에 정맥 철분제제의 사용

순천향대학교 의과대학 산부인과학교실

강미경·방성윤·김지영·박은희·김미경·최규연·이정재·이임순

Intravenous Iron in the Treatment of Postoperative Anemia Following Obstetric and Gynecologic Surgery

Mi Kyoung Kang, M.D., Seong Yun Bang, M.D., Ji Young Kim, M.D., Eun Hee Park, M.D., Mi Kyung Kim, M.D., Ku Yeon Choi, M.D., Jeong Jae Lee, M.D., Im Soon Lee, M.D.

Department of Obstetrics and Gynecology, College of Medicine, Soonchunhyang University, Seoul, Korea

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Iron Sucrose:

polynuclear iron(III)-hydroxide core complexed

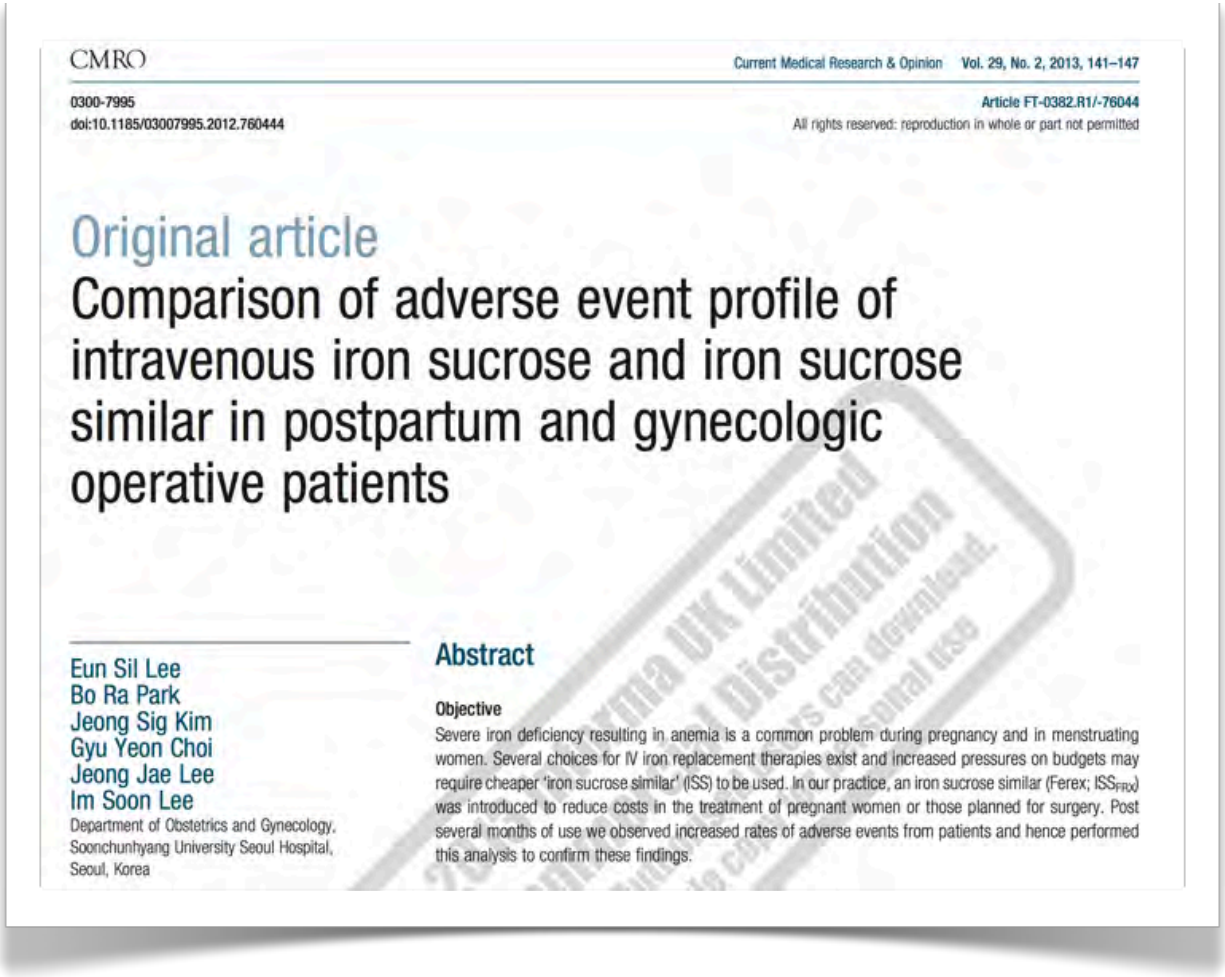
with sucrose in water

Non-Biological Complex Drug

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

13

Is Iron Sucrose Similar Safe for My Patients?



CMRO

Current Medical Research & Opinion Vol. 29, No. 2, 2013, 141–147

0300-7995
doi:10.1185/03007995.2012.760444

Article FT-0382.R1/-76044

Original article

Comparison of adverse event profile of intravenous iron sucrose and iron sucrose similar in postpartum and gynecologic operative patients

Eun Sil Lee
Bo Ra Park
Jeong Sig Kim
Gyu Yeon Choi
Jeong Jae Lee
Im Soon Lee
Department of Obstetrics and Gynecology, Soonchunhyang University Seoul Hospital, Seoul, Korea

Abstract

Objective

Severe iron deficiency resulting in anemia is a common problem during pregnancy and in menstruating women. Several choices for IV iron replacement therapies exist and increased pressures on budgets may require cheaper 'iron sucrose similar' (ISS) to be used. In our practice, an iron sucrose similar (Ferex; ISS_{FRX}) was introduced to reduce costs in the treatment of pregnant women or those planned for surgery. Post several months of use we observed increased rates of adverse events from patients and hence performed this analysis to confirm these findings.

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Study Design

- Determine the rate of adverse events with ISS
- ***Retrospective analysis*** of inpatients treated over a period of 4 years
- Patients with IDA
  - Post-pregnancy: natural birth or Cesarean sections
  - Post-Gy surgery: myomectomy, hysterectomy, cystectomy and adnexectomy
- Data collected for all treated patients in an anonymous manner with data points focusing on ***adverse events during and after injection of IV iron***
- Events from patients charts and all data double checked

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

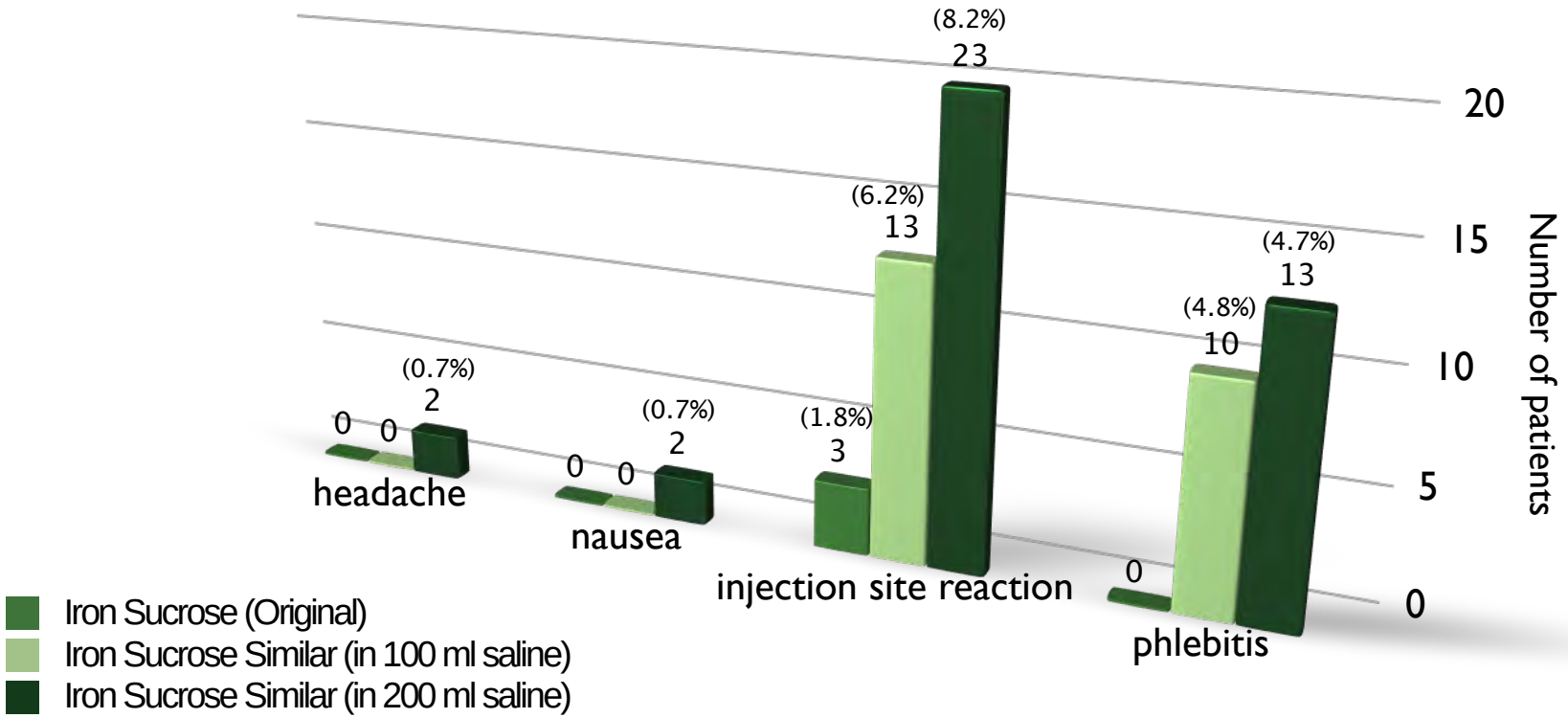
Patient Demographics

	IS_{ORIG}	ISS_{FRX}-100	ISS_{FRX}-200	*p*-value
Number of patients	169	210	279	
Age (years) (95% CI)	38.0 ± 9.7 (36.5–39.5)	38.5 ± 10.8 (37.0–39.9)	39.1 ± 10.6 (39.9–40.4)	0.536
Planned operation				0.002
Obstetric surgery	78	94	101	
Uterine surgery	76	74	118	
Other	15	42	59	
Baseline Hb (g/dL) before iron injection (95% CI)	8.8 ± 1.3 (8.6–9.0)	9.9 ± 1.7† (9.7–10.1)	10.3 ± 1.5† (10.1–10.5)	$p < 0.001$
Total iron doses (mg) (95% CI)	416 ± 184 (388.0–444.1)	498 ± 159† (476.4–519.8)	490 ± 198† (467.0–513.7)	$p < 0.001$

†Significantly different from IS_{ORIG} group.
IS_{ORIG}; iron sucrose originator (Venoferrum); ISS_{FRX}; iron sucrose similar (Ferex).

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Results



- ***Increased in adverse events*** with use of an ***ISS***
- The events were ***acute***

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Results

- Most events were considered relatively mild with minimal
- However it caused increase patient stress and reluctance for repeat treatment

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Comparison of Physicochemical Characteristics

Table 2. Physicochemical characteristics of the iron sucrose similar Ferex (ISSFRX) compared to the USP specifications for iron sucrose injection and the shelf -life specifications of iron sucrose originator (ISORIG) injection.

Parameter	USP*	IS_{ORIG} †	ISS_{FRX}		
Lot	–	–	FRX05-07003	FRX05-10001	FRX05-12001
Year of analysis	–	–	2008	2010	2012
Characteristics	–	Dark brown, opaque, aqueous solution	Dark brown, opaque, aqueous solution	Dark brown, opaque, aqueous solution	Dark brown, opaque, aqueous solution
pH	10.5–11.1	10.5–11.0	11.0	10.7	10.6
Titratable alkalinity (ml)	0.5–0.8	0.5–0.8	0.8	0.6	0.4
Turbidity point	4.4–5.3	4.7–5.3	5.2	4.9	4.7
Molecular weight					
Mw (Da)	34,000–60,000	34,000–54,000	38,100	39,000	37,600
Mn (Da)	≥24,000	24,000–36,000	28,900	28,800	28,200
P	≤1.7	≤1.7	1.3	1.4	1.3
Reduction potential (mV)					
Fe(III)/Fe(II)	−700 to −800	−700 to −800	−630	−680	−640
Fe(II)/Fe(0)	−1350 to −1450	−1350 to −1450	−1410	−1390	−1340

*United States Pharmacopeial Convention. Iron Sucrose Injection, Official monograph innThe United States Pharmacopeia. United States Pharmacopeial Convention: Rockville, 2008; Vol. 31, pp. 2449–2451.

†Shelf-life specification for IS_{ORIG} (iron sucrose injection).

Mw, weight average molecular weight; Mn, number average molecular weight; P, Mw/Mn ratio.

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Limitation and Questions

- Clinical efficacy could not be evaluated
  - Many patients only had Hb measurements prior to ISS / Venoferrum® and next measurement after surgery or pregnancy
  - Differences in patient baseline population
  - *Reduced efficacy in ISS group*[1]
- Unknown if additional toxicities as other assessments not conducted
  - *Animal studies: impact to heart, liver or kidney*[2]

1. Rottembourg J et al. Nephrol Dial Transplant 2011
2. Toblli JE et al. Inflamm Allergy Drug Targets 2012

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Clinical Data Demonstrate Differences between IS and ISS's

Study	Design	Key Results
Alejandro Martin-Malo et al. *Nephrol Dial Transplant* 2012	Assessed effects of both Venofer and ISS during the hemodialysis session in percentage of cells with ROS production, ICAM-1 and percentage apoptotic cells	Significant ***increase of oxidative stress in HD patients treated with ISS***: • The percentage of cells with reactive oxygen species production, ICAM-1 expression and apoptosis was significantly increased with generic iron compounds at T2 and T3 in comparison to the original iron sucrose (Venofer®)
Rottembourg J et al. *Nephrol Dial Transplant* 2011	Retrospective evaluation to assess the impact of the switch from the originator IS (Venofer®) to the ISS (FerMylan®) on Hb levels and iron parameters in CKD patients undergoing hemodialysis	**Switch to an ISS was associated with:** • **Significant reduction in Hb level** • **Reduced iron indices** • **Increased IV iron and ESA consumption** **Potential clinical implications of decrease in Hb level and shorter proportion of time spent within target Hb in population receiving an ISS.** **Both preparations showed a comparable safety profile**
Stein et al. *CMRO* 2012	3 case reports of IBD patients switched from iron sucrose (Venofer®) to an ISS	Patients experienced ***hypovolaemic dysregulation, urticaria, headache, peripheral edema post treatment with ISS.*** No adverse effects previously recorded with iron sucrose (Venofer®) adminstration

ROS, reactive oxygen species; ICAM-1, inter-cellular adhesion molecule-1; HD, hemodialysis
CKD, chronic kidney disease; ESA: erythropoiesis stimulating agent
CMRO, Current Medical Research and Opinion; IBD, inflammatory bowel disease

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Iron Sucrose

- Non-Biological Complex Drug -

Purification procedures

Starting materials [Iron sucrose (e.g. $FeCl_3$ or $Fe_2(SO_4)_3$); Base(e.g. NaOH, Na_2CO_3 or NH_3)]

Synthetic procedures

Concentrations of the reagents

pH of the reaction mixture at different stages of the synthesis

Reaction time

Reaction temperature

Modified from Professor Jacques Rottembourg. Presented at Fresenius Nephro Summit Berlin, 31 March 2012

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Iron Sucrose Similar

Iron Sucrose

not fully standardized
manufacturing process:
subtle structural modifications

- Release iron too rapidly into circulation
  - Oxidative stress
  - Inflammation
  - Endothelial damage
  - Hemodynamic alteration

Iron Sucrose Similar

☑ ***Safety***
☑ ***Efficacy***

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Conclusions

- ***ISS had more adverse events*** compared to originator iron sucrose (Venoferrum®)
- ***Iron reduction potentials*** of ISS didn't comply with the pharmacopeial specifications and didn't have standardized manufacturing process
- ***Subtle structural modifications*** may affect the stability of the iron complex, which can lead to difference in safety and efficacy
- ***ISS, copy of non-biological complex drug, should undergo a centralized approval process***, supervised by EMA and FDA.

SCH SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL

Thank You for Your Attention!

CMRO

Current Medical Research & Opinion Vol. 29, No. 2, 2013, 141–147

0300-7995
doi:10.1185/03007995.2012.760444

Article FT-0382.R1/-76044

Original article

Comparison of adv se e ent ofile of intravenous iron su ose nd n sucrose similar in postpart ar gyn ologic operative patients

Eun Sil Lee
Bo Ra Park
Jeong Sig Kim
Gyu Yeon Choi
Jeong Jae Lee
Im Soon Lee

Department of Obstetrics and Gynecology, Soonchunhyang University Seoul Hospital, Seoul, Korea

Abstract

Objective

Severe iron deficiency resulting in anemia is a common problem during pregnancy and in menstruating women. Several choices for IV iron replacement therapies exist and increased pressures on budgets may require cheaper 'iron sucrose similar' (ISS) to be used. In our practice, an iron sucrose similar (Ferex; ISS_{FRX}) was introduced to reduce costs in the treatment of pregnant women or those planned for surgery. Post several months of use we observed increased rates of adverse events from patients and hence performed this analysis to confirm these findings.

SOON CHUN HYANG UNIVERSITY HOSPITAL SEOUL