Intravenous iron infusion and newer non-dextran formulations

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ABSTRACT

There are several newer intravenous iron formulations to treat iron deficiency and its anaemia. Its use in the primary care setting has been infrequent compared to tertiary centres, due to historical concerns such as anaphylaxis. There is a lack of overall comparison among the intravenous formulations of iron. Compared to oral iron therapy, the newer intravenous formulations, which allow a complete or near-complete replacement in a single sitting of 15–30 minutes, have an improved safety profile with better tolerability, efficacy and effectiveness. They are suited for administration in the primary care setting. The four non-dextran formulations (ferric carboxymaltose, iron sucrose, iron isomaltoside and ferumoxytol) share an equal or near equal efficacy and safety profile. This article also outlines how to provide iron infusion safely and effectively in the community.

Iron is an essential element and nutrient for the human body functions. Iron deficiency (ID) and iron deficiency anaemia (IDA) are common health problems worldwide. The World Health Organization (2011) estimated 34% of the global population (>2 billion) is affected by anaemia. The most common type of anaemia was ID (50% of total anaemia), which primarily affected women of reproductive age and young children.[1]

Although the practice of intravenous (IV) iron to treat iron deficiency and its anaemia has existed for more than six decades,[2] its use in primary care centres has, compared to tertiary centres, not been widespread, largely due to historical concern of anaphylaxis and lack of remuneration. Administration of newer (non-dextran) iron formulations allows a complete or near-complete replacement in a single sitting of 15–30 minutes. These newer formulations have an improved safety profile and better tolerability, efficacy and effectiveness compared with oral iron therapy. They are suited for administration in primary care or community practices in a proper setting. This article outlines how to provide iron infusion safely and effectively, along with a brief comparison of the newer formulations (ferric carboxymaltose (FCM), iron sucrose (ISC), iron isomaltoside (IIM) and ferumoxytol (FOT)).

Although in most guidelines oral iron remains as a the first-line treatment for replacement of iron, its common side effects (gastric upset and constipation and the need to take it regularly for months to replenish iron stores) often result in non-adherence. Because intramuscular iron injection can cause pain and skin staining and require multiple injections with questionable absorption, it is therefore no longer favourable.

Indications and contraindications

Symptoms specific to ID are relatively uncommon but can include pagophagia (ice craving) or other forms of pica and restless-legs syndrome. Symptoms related to IDA are non-specific: they include fatigue,

weakness, tiredness, dizziness, irritability and pale skin, and in severe cases chest pain, palpitations or shortness of breath. Hair and nail disorders such as koilonychia (spoon nails) can also occur in chronic IDA. More importantly, the untreated ID and IDA can eventually impact on cognition, academic achievement, exercise tolerance, work productivity and quality of life.[3] ID and IDA should be confirmed by blood count and iron studies with correct interpretation. Although the details of investigation for IDA are beyond the scope of this article, it is always imperative to address the underlying cause while correcting the deficiency.

Figure 1: Indications for iron infusion.

- Malabsorption (coeliac disease, inflammatory bowel disease, weight-loss surgery, bowel resection)
- Inadequate diet (vegan, vegetarian)
- Excess blood loss (chronic occult bleeding, excess menstrual blood loss, childbirth)
- Increased body demand (pregnancy of beyond first trimester, rapid growth)
- Anaemia of chronic disease/inflammation (chronic kidney disease, cancers, rheumatoid arthritis, heart failure), in which functional iron deficiency (FID)† can be present
- Intolerance, poor adherence or unresponsiveness to oral iron

†FID denotes a state in which there is insufficient iron mobilisation for erythropoiesis despite normal or high ferritin concentrations with a low transferrin saturation reflecting inadequate iron availability. Maintaining the ferritin level greater than 100–200µg/L in some chronic conditions, such as heart failure, is important to improve ventricular function, quality of life and to reduce hospitalisations.[7,8]

Figure 2: Contraindications for iron infusion.

- Anaemia not caused by iron deficiency
- Known anaphylaxis to the specific iron product
- Iron overload conditions (haemochromatosis, hemosiderosis, thalassemia major)
- High-risk patients with serious comorbidities (moderate to severe failure of the heart, liver or respiratory system); such individuals could be managed at tertiary facilities

Infusion offers an alternative route of administration for those in whom oral iron is unsuitable due to intolerance, poor adherence, impracticality or contraindications. Indications for iron infusion include ID and IDA caused by the underlying conditions described in Figure 1.[4-6] Figure 2 lists contraindication for infusion.[4-6] Precautions include individuals with acute infection, asthma, marked atopy, liver dysfunction or conditions associated with low phosphate in the body. There are insufficient data to support the safety of iron infusion in the first trimester of pregnancy and in children under 14 years of age. Nevertheless, trial infusions of ferric carboxymaltose, iron sucrose and ferumoxytol in children (<14 years) at tertiary centres have shown some promises and is going to have further evaluation. [9–15]

Benefits

Intravenous iron rapidly restores iron and expedites haemoglobin synthesis. Newer formulations (Table 1) contain carbohydrate cores that more tightly bind elemental iron, allowing for a much slower release and providing marginal or fewer reactions.[1,16] They have also demonstrated greater efficacy and effectiveness and, compared to oral therapy and previous parenteral formulations, can improve quality of life and productivity. [6,17,18] Newer formulations also have the potential save health costs by reducing the frequency of visits to hospital and healthcare providers.[18–21] Some studies have indicated that the newer generations of intravenous iron are underutilised due to historical fears about anaphylaxis that were far more common with high molecular weight iron dextrans (eg, imferon, dexferrum), which are no longer available.[16,19] Two narrative reviews and one meta-analysis have suggested a reconsideration of the current paradigm whereby oral iron treatment is considered a first-line therapy;[16,19,22] it needs further evaluation with a broad consensus. There are greater than 20 randomised studies in which IV administration of iron offers better tolerability, efficacy and effectiveness compared to oral iron.[23–28] One randomised control trial in Australia described the cost of IV use as no more than the cost for oral therapy, in addition to having superior tolerance, efficacy and effectiveness.[29]

Adverse effects

- Anaphylaxis is rare but can be life threatening if not managed properly.[21] It involves bronchospasm with dyspnoea, angioedema, tachycardia and hypotension. Rates vary according to iron formulation: FCM and ISC (1–10/10,000 cases (≈0.1%–0.01%), IPC (10–100/10,000 cases).[6,30] Two review studies, one of which was a meta-analysis, reported that a properly defined serious anaphylaxis are even less than the above rate, if dextran is excluded and drug therapy (adrenaline, antihistamine) is given for minor reactions in the context of practitioners' fears for further deterioration, which is not uncommon.[31,32]

Less severe or minor reactions include:

- Facial flushing, urticaria, arthralgia, myalgia, sensation of stiffness in face or limbs.
- Dizziness, headache, nausea, dysgeusia.
- Injection site reactions (pain, discoloration of skin). Skin staining usually fades over time, but may be permanent, in which case laser therapy could be considered.[33] It may become a serious issue in young women. See Figure 3 on how to avoid or minimise such an incidence and others.
- Delayed symptoms may occur one- or two-days post infusion: chills and fever, headache, arthralgia, myalgia, urticaria/rash, angioneurotic oedema.
- Transient hypophosphatemia may also occur, particularly with FCM.[30,34]

Dosage

The Ganzoni formula (created by Dr Ganzoni of Zurich) usefully estimates a replacement dosage of parenteral iron required (Table 2).[35] However, a simplified method of calculation based on current haemoglobin level and body weight can also be used if preferred (Table 2). Each iron product has specific instructions for dilution and duration of infusion, so refer to the specific instruction or local guidelines for each product whenever possible. Generally, FCM (1,000mg) and IIM (1,000–1,500mg) can be given as a single dose over 15–30 minutes.[36] As per manufacturer, FOT is to be given 510mg at a time; two trials of 1,020mg infusion over 15–30mins reported

Table 1: History of parenteral iron products.[1,18,19]

Year	Iron products
Before 1954	Ferric hydroxide and iron saccharide (severe reactions and toxicity).
1954	Iron dextran (IDX): *Imferon* (high molecular weight) withdrawn in 1991.
1992–1997	Iron dextran (IDX): *INFeD* (low molecular weight), *Dexferrum* (high molecular weight, withdrawn in 2009), *Infufer* (low molecular weight). Unavailable in Australasia.
1990s	Iron polymaltose complex (IPC): *Ferrosig, Ferrum H*. Note: the oral formulation of IPC has been available since 1978.
1999	Ferric gluconate (FGC): *Ferrlecit*.
Newer formulations	
2000	Iron sucrose (ISC):† *Venofer.*
2001	Iron dextran (IDX): *Cosmofer* (low molecular weight). Unavailable in Australasia.
2009–2010	Ferumoxytol (FOT): *Feraheme.* Iron isomaltoside (IIM):† *Monofer.* Ferric carboxymaltose (FCM):† *Ferinject.*

† = Approved by Medsafe and subsided by PHARMAC in New Zealand.

no safety concerns, but this needs further appraisal.[37,38] ISC requires multiple fraction doses with 100–200mg maximum at a time, which is commonly used in renal dialysis patients.

Comparison

A literature search of comparison studies for four non-dextran formulations (FCM, ISC, IIM and FOT) yielded a total of 22 head-to-head comparisons (n=10,269) and three multi-comparisons (more than two products).[39–63] The comparisons included various types of studies, such as randomised and clinical trials, cohorts and reviews. The subjects were IDA patients with any cause, such as diet, childbearing and menorrhagia, gastrointestinal disorders, renal failure and cancer. The overall analysis revealed that those four formulations share a comparable safety profile and efficacy overall. However, products that can deliver a replacement with a single large dose rapidly increase blood parameters and offers a more convenient dosing regimen. Hypophosphatemia can be encountered infrequently with FCM and its long-term clinical significance is unknown due to lack of study. Appendix Table 1 illustrates details of comparison with total numbers, methods and subjects of studies.

Figure 3: Preparation and administration of intravenous iron.

- The iron ampoules/vials should be stored below 25–30°Celcius and protected from light. Do not refrigerate nor freeze.
- Obtain informed consent after discussing the pros and cons of the procedure.
- The ideal solution for dilution is 0.9% isotonic saline, as not all formulations are compatible with dextrose. Dilution amount for drip infusion is 250ml–500ml, and 10ml–20ml for IV push/bolus.
- Use aseptic technique (as for venepuncture).
- Keep a resuscitation kit (including adrenaline) nearby in case of anaphylaxis.
- Adverse reactions can be minimised with a slower infusion rate, particularly in the initial stages. Consider taking 30 minutes, instead of 15 minutes, and using a drip infusion instead of an IV bolus.
- The injector should be seated in a comfortable position if elected for slow IV bolus.
- Take appropriate observations during the infusion.
- To avoid or minimise skin staining, you must prevent extravasation by ensuring the IV canula is inside the vein at the insertion site by initially running saline fluid and then, at the end of the infusion, flushing with 20–50mL of saline fluid and applying an instant compression pressure with cover. Do not rub or massage over the IV/infusion site.
- Do not attempt for IV iron administration without being trained for IV canula insertion and proper setup.

Table 2: Ganzoni formula and simplified method of calculation for iron dosage.

Ganzoni formula		
Total iron deficit/requirement (mg) = {body weight (kg) x (target Hb – actual Hb in g/L)} x 0.24 + iron depot (500mg). *Example of calculation for a patient with an ideal body weight of 60 kg and Hb = 80g/L, and the target Hb is set to be 150 g/L. The total required iron dose = {60 x (150 - 80)} x 0.24 + 500 mg = 1508 mg (1500 mg).*		
Simplified method of calculation for iron dosage		
Hb g/L	Body weight 35 to <70Kg	Body weight ≥70 kg
<100 g/L	1,500 mg	2,000 mg
≥100 g/L	1,000 mg	1,500 mg

Discussion and conclusion

Apparently, iron infusion with those newer formulations has a better safety profile than old dextran iron and can provide a more convenient and effective alternative to adhering to months of oral iron replacement. Overall, there is little current evidence to recommend a single best iron product for infusion among the four non-dextran products. However, formulations that can deliver a replacement with a single large dose would be more convenient and require fewer visits to healthcare providers. Although anaphylactic reactions are rare with newer non-dextran formulations, close monitoring during administration is recommended for infusion with all IV iron products. Choice of product will be determined by local availability/ guidelines, cost and convenience.

Key points:

- Modern intravenous iron formulations offer an improved safety profile with better tolerability, efficacy and effectiveness compared to oral iron therapy.
- There is no strong current evidence to recommend a single best iron product for infusion among the four non-dextran formulations.
- Choice of iron product for infusion will depend on local availability/ guidelines, cost and convenience.
- Two narrative reviews and one meta-analysis suggested a reconsideration of the current paradigm whereby oral iron treatment is considered a first-line therapy; it needs further evaluation.

Appendix

Appendix Table 1: Head-to-head comparison of non-dextran intravenous iron formulations.

	Year of publication	Type of study	Sample number	Note
FCM vs ISC				
1.	Lee et al (2019)[39]	Randomized open-label, multicentre	101	Menorrhagia patients
2.	Laso-Morales et al (2019)[40]	RCT	48	Colorectal cancer patients
3.	Mahey et al (2017)[41]	RCT	30	Gynaecological patients
4.	Jose et al (2019)[42]	Randomized clinical trial	100	Pregnant women
5.	Naqash et al (2018)[43]	Phase IV clinical trails	200	IDA in normal women
6.	Christoph et al (2012)[44]	Cohort (retrospective)	206	Pregnant women
7.	Sharma et al (2017)[45]	Cohort (prospective)	120	Post-partum anaemia.
8.	Bisbe et al (2011)[46]	Cohort, multicentre comparative	76	Surgical patients
9.	Hofman et al (2018)[47]	Cohort (retrospective)	221	Renal patients
		Total (n)	**1102**	
FCM vs IIM				
1.	Ehlken et al (2019)[48]	Cohort retrospective (FCM 309 + IIM 339)	748	Data extraction (2014-2017)
2.	Mulder et al (2019)[49]	Cohort (single-centre)	1334	IDA of any cause
3.	Wolf et al (2020)[50]	Randomized clinical trials	123	IDA of normal adult.
4.	Pollock et al (2019)[51]	Systematic review on RCTs	19	Indirect comparison
			2224	
FCM vs FOT				
1.	Adkinson et al (2018)[52]	Randomized, multicenter, double-blind clinical trial	1997	IDA of any cause
		Total (n)	**1997**	
ISC vs IIM				
1.	Bhandari et al (2015)[53]	Randomized open-label	351	Renal patients
2.	Auerbach et al (2019)[54]	Prospective, multi-center, randomized comparison	1512	IDA in normal adult
3.	Derman et al (2017)[55]	Randomized open-label, comparative, multi-center trial	511	IDA of any cause
4.	Derman et al (2018)[56]	Randomized trial	248	Gynaecology patients
5.	Bhandari et al (2020)[57]	Randomized, open-label,	1538	Renal patients
		Total (n)	**4160**	
ISC vs FOT				
1.	Macdougall et al (2014)[58]	Randomized, open-label, multicentre	162	Renal patients
2.	Hetzel et al (2014)[59]	Randomized, open-label	605	IDA of any cause
3.	Strauss et al (2016)[60]	RCTs, post-hoc analysis	767	Renal patients + IDA of any cause
		Total (n)	**1534**	
		Grand Total (n)	**10269**	

ISC= iron sucrose, FCM= ferric carboxymaltose, IIM= iron isomaltoside (aks ferric derisomaltose), FOT= Ferumoxytol.

Competing interests:
Nil.

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REFERENCES

1. World Health Organization. The global prevalence of anemia in 2011. Geneva: WHO; 2015. ISBN 978 92 4 156496 0.
2. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. Hematology Am Soc Hematol Educ Program. 2010;2010:338-47. doi: 10.1182/asheducation-2010.1.338.
3. Zhang E, Tattersal SJN. Iron deficiency anemia in adults: update. MedicineToday (Aust). 2019 Oct; Vol 20 (10): 27-34.
4. Baird-Gunning J, Bromley J. Correcting iron deficiency. Aust Prescriber 2017;40:41. doi: 10.18773/austprescr.2016.096.
5. Simpson J, Ross B, De Malmanche J. Iron deficiency: how to detect it, how to correct it. Medicine Today 2017; 18(10): 40-50.
6. South Australian Perinatal Practice Guidelines. Iron infusion. Approved SA Health Safety & Quality Strategic Governance Committee 19/04/2016. www.sahealth.sa.gov.au/wps/wcm/connect/. Accessed 16/05/2020.
7. Dinatolo E, Dasseni N, Metra M, Lombardi C, von Haehling S. Iron deficiency in heart failure. J Cardiovasc Med (Hagerstown). 2018 Dec;19(12):706-716. doi: 10.2459/JCM.0000000000000686.
8. Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. Circulation. 2018 Jul 3;138(1):80-98. doi: 10.1161/CIRCULATIONAHA.118.030099.
9. Tan MLN, Windscheif PM, Thornton G, Gaynor E, Rodrigues A, Howarth L. Retrospective review of effectiveness and safety of intravenous ferric carboxymaltose given to children with iron deficiency anemia in one UK tertiary centre. Eur J Pediatr. 2017 Oct;176(10):1419-1423. doi: 10.1007/s00431-017-2995-8.
10. Powers JM, Shamoun M, McCavit TL, Adix L, Buchanan GR. Intravenous Ferric Carboxymaltose in Children with Iron Deficiency Anemia Who Respond Poorly to Oral Iron. J Pediatr. 2017 Jan;180:212-216. doi: 10.1016/j.jpeds.2016.09.053.
11. Kaneva K, Chow E, Rosenfield CG, Kelly MJ. Intravenous iron sucrose for children with iron deficiency anemia. J Pediatr Hematol Oncol. 2017 Jul;39(5):e259-e262. doi: 10.1097/MPH.0000000000000879.
12. Stein RE, Plantz K, Maxwell EC, Mamula P, Baldassano RN. Intravenous iron sucrose for treatment of iron deficiency anemia in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2018 Feb;66(2):e51-e55. doi: 10.1097/MPG.0000000000001684.
13. Sabe R, Vatsayan A, Mahran A, Khalili AS, Ahuja S, Sferra TJ. Safety and efficacy of intravenous iron sucrose for iron-deficiency anemia in children and adolescents with inflammatory bowel disease. Glob Pediatr Health. 2019 Aug 18;6:2333794X19870981. doi: 10.1177/2333794X19870981.
14. Hassan N, Boville B, Reischmann D, Ndika A, Sterken D, Kovey K. Intravenous Ferumoxytol in Pediatric Patients with Iron Deficiency Anemia. Ann Pharmacother. 2017 Jul;51(7):548-554. doi: 10.1177/1060028017699429.
15. Hassan N, Cahill J, Rajasekaran S, Kovey K. Ferumoxytol infusion in

pediatric patients with gastrointestinal disorders: first case series. Ann Pharmacother. 2011 Dec;45(12):e63. doi: 10.1345/aph.1Q283.

16. Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. Blood Transfus. 2014 Jul;12(3):296-300. doi: 10.2450/2014.0094-14.
17. Strauss WE, Auerbach M. Health-related quality of life in patients with iron deficiency anemia: impact of treatment with intravenous iron. Patient Relat Outcome Meas. 2018 Aug 27;9:285-298. doi: 10.2147/PROM.S169653.
18. Auerbach M, Macdougall I. The available intravenous iron formulations: History, efficacy, and toxicology. Hemodial Int. 2017 Jun;21 Suppl 1:S83-S92. doi: 10.1111/hdi.12560.
19. Cançado RD, Muñoz M. Intravenous iron therapy: how far have we come? Rev Bras Hematol Hemoter. 2011;33(6):461-9. doi: 10.5581/1516-8484.20110123.
20. Radhika AG, Sharma AK, Perumal V, et al. Parenteral Versus Oral Iron for Treatment of Iron Deficiency Anemia During Pregnancy and post-partum: A Systematic Review. J Obstet Gynaecol India. 2019 Feb;69(1):13-24. doi: 10.1007/s13224-018-1191-8.
21. Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica. 2014 Nov;99(11):1671-6. doi: 10.3324/haematol.2014.111492.
22. Auerbach M, Gafter-Gvili A, Macdougall IC. Intravenous iron: a framework for changing the management of iron deficiency. Lancet Haematol. 2020 Apr;7(4):e342-e350. doi: 10.1016/S2352-3026(19)30264-9.
23. Qunibi WY, Martinez C, Smith M, Benjamin J, Mangione A, Roger SD. A randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron for treatment of iron deficiency anemia of non-dialysis-dependent chronic kidney disease patients. Nephrol Dial Transplant. 2011 May;26(5):1599-607. doi: 10.1093/ndt/gfq613.
24. Shim JY, Kim MY, Kim YJ, Lee Y, Lee JJ, et al. Efficacy and safety of ferric carboxymaltose versus ferrous sulfate for iron deficiency anemia during pregnancy: subgroup analysis of Korean women. BMC Pregnancy Childbirth. 2018 Aug 28;18(1):349. doi: 10.1186/s12884-018-1817-y.
25. Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J, et al. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP). J Perinat Med. 2017 May 24;45(4):443-453. doi: 10.1515/jpm-2016-0050.
26. Bhavi SB, Jaju PB. Intravenous iron sucrose v/s oral ferrous fumarate for treatment of anemia in pregnancy. A randomized controlled trial. BMC Pregnancy Childbirth. 2017 May 8;17(1):137. doi: 10.1186/s12884-017-1313-9.
27. Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, Dekker G. Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: a randomized trial. J Matern Fetal Neonatal Med. 2013 May;26(7):654-9. doi: 10.3109/14767058.2012.746299.
28. Vadhan-Raj S, Strauss W, Ford D, Bernard K, Boccia R, Li J, Allen LF. Efficacy and safety of IV ferumoxytol for adults with iron deficiency anemia previously unresponsive to or unable to tolerate oral iron. Am J Hematol. 2014 Jan;89(1):7-12. doi: 10.1002/ajh.23582.
29. Khalafallah AA, Hyppa A, Chuang A, Hanna F, Wilson E, Kwok C. A Prospective Randomised Controlled Trial of a Single Intravenous Infusion of Ferric Carboxymaltose vs Single Intravenous Iron Polymaltose or Daily Oral Ferrous Sulphate in the Treatment of Iron Deficiency Anemia in Pregnancy. Semin Hematol. 2018 Oct;55(4):223-234. doi: 10.1053/j.seminhematol.2018.04.006.
30. Hardy S, Vandemergel X. Intravenous iron administration and hypophosphatemia in clinical practice. Int J Rheumatol. 2015;2015:468675. doi: 10.1155/2015/468675.
31. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015 Jan;90(1):12-23. doi: 10.1016/j.mayocp.2014.10.007.
32. DeLoughery TG. Safety of Oral and Intravenous Iron. Acta Haematol. 2019;142(1):8-12. doi: 10.1159/000496966.
33. Canning ML, Gilmore KA. Iron stain following an intravenous iron infusion. Med J Aust. 2017 Jul 17;207(2):58. doi: 10.5694/mja17.00040.
34. Adkinson NF, Strauss WE, Macdougall IC, Bernard KE, Auerbach M,5, Kaper RF, et al. Comparative safety of

intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial. Am J Hematol. 2018 May;93(5):683-690. doi: 10.1002/ajh.25060.

35. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. Schweiz Med Wochenschr. 1970 Feb 14;100(7):301-3.
36. National blood authority (Australia). Iron products and dose calculation choice for adults: guidance for Australian health providers. 2016 March. www.blood.gov.au/... 20052016.pdf. accessed 18/018/2020.
37. Auerbach M, Strauss W, Auerbach S, Rineer S, Bahrain H. Safety and efficacy of total dose infusion of 1,020 mg of ferumoxytol administered over 15 min. Am J Hematol. 2013 Nov;88(11):944-7. doi: 10.1002/ajh.23534.
38. Karki NR, Auerbach M. Single total dose infusion of ferumoxytol (1020 mg in 30 minutes) is an improved method of administration of intravenous iron. Am J Hematol. 2019 Jun 2. doi: 10.1002/ajh.25548.
39. Lee S, Ryu KJ, Lee ES, Lee KH, Lee JJ, Kim T. Comparative efficacy and safety of intravenous ferric carboxymaltose and iron sucrose for the treatment of preoperative anemia in patients with menorrhagia: An open-label, multicenter, randomized study. J Obstet Gynaecol Res. 2019 Apr;45(4):858-864. doi: 10.1111/jog.13893.
40. Laso-Morales MJ, Vives R, Vallejo-Tarrat A, Caló N, Valle-Beltran A, Pontes C. Single dose of intravenous ferric carboxymaltose infusion versus multiple fractionated doses of intravenous iron sucrose in the treatment of postoperative anemia in colorectal cancer patients: study protocol for a randomised controlled trial. Trials. 2019 Jan 7;20(1):23. doi: 10.1186/s13063-018-3125-2.
41. Mahey R, Kriplani A, Mogili KD, Bhatla N, Kachhawa G, Saxena R. Randomized controlled trial comparing ferric carboxymaltose and iron sucrose for treatment of iron deficiency anemia due to abnormal uterine bleeding. Int J Gynaecol Obstet. 2016 Apr;133(1):43-8. doi: 10.1016/j.ijgo.2015.09.007.
42. Jose A, Mahey R, Sharma JB, et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial. BMC Pregnancy Childbirth. 2019 Feb 4;19(1):54. doi: 10.1186/s12884-019-2200-3.
43. Naqash A, Ara R, Bader GN. Effectiveness and safety of ferric carboxymaltose compared to iron sucrose in women with iron deficiency anemia: phase IV clinical trials. BMC Womens Health. 2018 Jan 5;18(1):6. doi: 10.1186/s12905-017-0506-8.
44. Christoph P, Schuller C, Studer H, Irion O, De Tejada BM, Surbek D. Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. J Perinat Med. 2012 May 13;40(5):469-74. doi: 10.1515/jpm-2011-0231.
45. Sharma N, Thiek JL, Natung T, Ahanthem SS. Comparative Study of Efficacy and Safety of Ferric Carboxymaltose Versus Iron Sucrose in Post-partum Anemia. J Obstet Gynaecol India. 2017 Aug;67(4):253-257. doi: 10.1007/s13224-017-0971-x.
46. Bisbe E, García-Erce JA, Díez-Lobo AI, Muñoz M; Anemia Working Group España. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anemia in patients undergoing major elective surgery. Br J Anaesth. 2011 Sep;107(3):477-8. doi: 10.1093/bja/aer242.
47. Hofman JMG, Eisenga MF, Diepenbroek A, Nolte IM, van Dam B, Westerhuis R, Bakker SJL, Franssen CFM, Gaillard CAJM. Switching iron sucrose to ferric carboxymaltose associates to better control of iron status in hemodialysis patients. BMC Nephrol. 2018 Sep 20;19(1):242. doi: 10.1186/s12882-018-1045-8.
48. Ehlken B, Nathell L, Gohlke A, Bocuk D, Toussi M, Wohlfeil S. Evaluation of the Reported Rates of Severe Hypersensitivity Reactions Associated with Ferric Carboxymaltose and Iron (III) Isomaltoside 1000 in Europe Based on Data from EudraVigilance and VigiBase™ between 2014 and 2017. Drug Saf. 2019 Mar;42(3):463-471. doi: 10.1007/s40264-018-0769-5.
49. Mulder MB, van den Hoek HL, Birnie E, van Tilburg AJP, Westerman EM. Comparison of hypersensitivity reactions of intravenous iron: iron isomaltoside-1000 (Monofer®) versus ferric carboxy-maltose (Ferinject®). A single center, cohort study. Br J Clin Pharmacol. 2019 Feb;85(2):385-392. doi: 10.1111/bcp.13805.
50. Wolf M, Rubin J, Achebe M, Econs MJ, Peacock M, Imel EA, et al. Effects of Iron Isomaltoside vs Ferric Carboxymaltose

on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials. .JAMA. 2020 Feb 4;323(5):432-443. doi: 10.1001/jama.2019.22450.

51. Pollock RF, Muduma G. A systematic literature review and indirect comparison of iron isomaltoside and ferric carboxymaltose in iron deficiency anemia after failure or intolerance of oral iron treatment. Expert Rev Hematol. 2019 Feb;12(2):129-136. doi: 10.1080/17474086.2019.1575202.
52. Adkinson NF, Strauss WE, Macdougall IC, Bernard KE, Auerbach M,5, Kaper RF, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial. Am J Hematol. 2018 May;93(5):683-690. doi: 10.1002/ajh.25060.
53. Bhandari S, Kalra PA, Kothari J, Ambühl PM, Christensen JH, Essaian AM, et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venofer®) as maintenance therapy in haemodialysis patients. Nephrol Dial Transplant. 2015 Sep;30(9):1577-89. doi: 10.1093/ndt/gfv096.
54. Auerbach M, Henry D, Derman RJ, Achebe MM, Thomsen LL, Glaspy J. A prospective, multi-center, randomized comparison of iron isomaltoside 1000 versus iron sucrose in patients with iron deficiency anemia; the FERWON-IDA trial. Am J Hematol. 2019 Sep;94(9):1007-1014. doi: 10.1002/ajh.25564.
55. Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. Am J Hematol. 2017 Mar;92(3):286-291. doi: 10.1002/ajh.24633.
56. Derman R, Roman E, Smith-Nguyen GN, Achebe MM, Thomsen LL, Auerbach M. Iron isomaltoside is superior to iron sucrose in increasing hemoglobin in gynecological patients with iron deficiency anemia. Am J Hematol. 2018 Jun;93(6):E148-E150. doi: 10.1002/ajh.25094.
57. Bhandari S, Kalra PA, Berkowitz M, Belo D, Thomsen LL, Wolf M. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. Nephrol Dial Transplant. 2020 Feb 12. pii: gfaa011. doi: 10.1093/ndt/gfaa011.
58. Macdougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. Clin J Am Soc Nephrol. 2014 Apr;9(4):705-12. doi: 10.2215/CJN.05320513.
59. Hetzel D, Strauss W, Bernard K, Li Z, Urboniene A, Allen LF. A Phase III, randomized, open-label trial of ferumoxytol compared with iron sucrose for the treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy. Am J Hematol. 2014 Jun;89(6):646-50. doi: 10.1002/ajh.23712.
60. Strauss WE, Dahl NV, Li Z, Lau G, Allen LF. Ferumoxytol versus iron sucrose treatment: a post-hoc analysis of randomized controlled trials in patients with varying renal function and iron deficiency anemia. BMC Hematol. 2016 Jul 26;16:20. doi: 10.1186/s12878-016-0060-x.
61. Pollock RF, Biggar P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. Expert Rev Hematol. 2020 Feb;13(2):187-195. doi: 10.1080/17474086.2020.1709437.
62. Aksan A, Işık H, Radeke HH, Dignass A, Stein J. Systematic review with network meta-analysis: comparative efficacy and tolerability of different intravenous iron formulations for the treatment of iron deficiency anemia in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2017 May;45(10):1303-1318. doi: 10.1111/apt.14043.
63. Wetmore JB, Weinhandl ED, Zhou J, Gilbertson DT. Relative Incidence of Acute Adverse Events with Ferumoxytol Compared to Other Intravenous Iron Compounds: A Matched Cohort Study. PLoS One. 2017 Jan 30;12(1):e0171098. doi: 10.1371/journal.pone.0171098.