Original Article

Intravenous iron therapy in a rural hospital: A retrospective chart review

Ribal Kattini[1], Jenna Poirier, BSc[1], Lauren Minty, MD[2], Danielle LaJuenesse, RPh[3], Len Kelly, Md, M Clin Sci, FCFP, FRRM[3], Sharen Madden MD, MSc[4], Robert Minty, MD, FCFP[4], Sydney Larsen, MD[2], Ruben Hummelen, MD, PhD[4]

[1]Sioux Lookout Local Education Group, Sioux Lookout, ON, Canada, [2]Northern Ontario School of Medicine, Thunder Bay, ON, Canada, [3]Sioux Lookout Meno Ya Win He-alth Centre, Sioux Lookout, ON, Canada, [4]Division of Clinical Sciences, Northern Ontario School of Medicine, Thunder Bay, ON, Canada

Correspondence to: Len Kelly, lkelly@mcmaster.ca

This article has been peer reviewed.

Access this article online

Quick Response Code:

Website: www.cjrm.ca

DOI: 10.4103/CJRM.CJRM_4_20

Abstract

Introduction: Intravenous iron infusion therapy is commonly delivered in rural hospitals, but there are no common guidelines for dosing or choice of agent. The objective of the study was to understand present practice and alternate therapies and develop practical recommendations for small hospital use.

Methods: This was a retrospective chart review of all non-dialysis patients aged 15 years or older who received iron replacement therapy at Sioux Lookout Meno Ya Win Health Centre from May 2013 to May 2019 and a literature review of available iron preparations.

Results: Of the 147 patients who received intravenous iron replacement, 75 were administered a single dose of 200 mg or 500 mg iron sucrose. Commonly used in pregnant patients, an increase in haemoglobin by an average of 9.2 g/L followed a 200 mg dose and 12.5 g/L after 500 mg. The 3-h infusion time for the 500 mg dose consumed considerably more nursing resources. Non-pregnant patients can be transfused more effectively with iron maltoside which can efficiently deliver larger doses of iron.

Conclusion: We recommend iron maltoside for efficient intravenous iron replacement in non-pregnant patients and single or multiple doses of 200 mg iron sucrose during pregnancy.

Keywords: Intravenous iron infusion therapy, iron maltoside, rural medicine

Résumé

Introduction: La perfusion intraveineuse de fer est fréquente dans les hôpitaux ruraux, mais il n'existe pas de lignes directrices courantes sur la posologie ou le choix de l'agent. Cette étude visait à comprendre la pratique actuelle, et les autres options thérapeutiques et d'émettre des recommandations pratiques à l'intention des petits hôpitaux.

Méthodologie: Revue rétrospective des dossiers de tous les patients de 15 ans et plus non sous dialyse qui avaient reçu une supplémentation en fer à l'Hôpital SLMHC entre les mois de mai 2013 et mai 2019 et revue de la littérature sur les préparations de fer commercialisées.

Résultats: Sur les 147 patients ayant reçu une perfusion de supplémentation en fer, 75 ont reçu une dose unique de 200 mg ou de 500 mg de fer-saccharose. Fréquemment utilisées chez les femmes enceintes, les doses de 200 et de 500 mg ont augmenté le taux d'Hb d'en moyenne 9,2 g/L et de 12.5 g/L, respectivement. La perfusion de 3 heures nécessaire à la dose de 500 mg a utilisé considérablement

Received: 23-01-2021 **Revised:** 01-04-2021 **Accepted:** 01-05-2021 **Published:** 02-07-2021

How to cite this article: Kattini R, Poirier J, Minty L, LaJuenesse D, Kelly L, Madden S, *et al*. Intravenous iron therapy in a rural hospital: A retrospective chart review. Can J Rural Med 2021;26:123-7.

plus de ressources infirmières. Le fer-isomaltoside, qui administre efficacement des doses supérieures de fer, est perfusé plus efficacement chez les patients, à l'exclusion des femmes enceintes.
Conclusion: Nous recommandons le fer-isomaltoside pour la supplémentation en fer efficace chez les patients, à l'exclusion des femmes enceintes et une dose unique ou multiple de 200 mg de fer-saccharose durant la grossesse.

Mots-clés: Fer-isomaltoside, médecine rurale, perfusion intraveineuse de fer

INTRODUCTION

Intravenous iron is a useful and rapid treatment of iron deficiency anaemia for patients who have failed or cannot tolerate oral iron therapy and it reduces the need for blood transfusions.[1] Iron replacement therapies vary; small rural hospitals must navigate options of multiple agents, doses and infusion rates.[2] Oral iron replacement is sufficient for most patients with iron deficiency anaemia, but for patients within 6 weeks of elective surgery or parturition, intravenous iron may be needed for a more rapid treatment.[1]

Previous generations of intravenous iron preparations were associated with adverse side effects including anaphylaxis, now rare with newer formulations. These bind iron more closely to the carbohydrate molecule, resulting in less free iron and fewer adverse reactions. The risk of anaphylaxis with first exposure to iron sucrose is <1:250,000 versus 1:50,000 for a blood transfusion, which carries the additional risk of transmission of infectious disease.[3-6]

A decade ago, physicians at the Sioux Lookout Meno Ya Win Health Centre (SLMHC) were using a variety of formulations for iron replacement therapy. In 2013, this was standardised to the use of a single agent, iron sucrose, chosen for its safety profile, ease of administration, lack of a required test dose and alignment with medication coverage by the Non-Insured Health Benefits Programme (NIHB), so that similar agents were available both in hospital and remote nursing stations.[2,7] Doses included both standard (200 mg) and high dose (500 mg) infusions.[8,9] This report presents the results of 6 years of single-dose iron infusion data. We list the intravenous iron preparations presently available in Canada and discuss issues for ongoing protocol development, including multiple dose requirements.

METHODS

SLMHC provides medical and laboratory services to a catchment of 29,000 primarily First Nations patients in the town of Sioux Lookout and 26 northern communities. The setting is unique as patients often travel distances of over 300 km from their remote community by fixed wing airplane to access surgery or obstetrical care.[9] Obstetrical patients late in a pregnancy or pre-operative patients <6 weeks with iron-deficient anaemia who are newly diagnosed or have failed oral therapy often require effective iron replacement.[10-13]

A retrospective chart review of all non-dialysis patients aged 15 years or older who received iron replacement therapy at SLMHC from May 2013 to May 2019 was undertaken. Data included patient demographics, diagnosis, dose, infusion duration and adverse effects, baseline and follow-up haemoglobin (Hb) at 7–30 days, mean corpuscular volume (MCV) and ferritin. The focus was on the relative effectiveness of 200 mg versus 500 mg doses of iron sucrose.

Data on single and multiple-dose infusions were collected, but analysis was limited to data on single-dose infusions. Patients were excluded if they had no follow-up blood work within 7–30 days of treatment. Iron infusion and dispensing data were collected from hospital charts and from the hospital pharmacy dispensing programme. Adverse events were documented by SLMHC staff; the protocol for patients receiving intravenous iron requires constant nursing observations and vital signs every 15 min. Ethics approval was granted by the SLMHC Research Review and Ethics Committee.

RESULTS

A total of 147 patients received intravenous iron replacement. Patients (n=18) with no recorded follow-up blood work 7–30-day post-infusion were excluded. Of the remaining 129 patients, 75 received a single dose infusion and 54 received multiple doses. The average time of follow-up Hb post-infusion was 18 days (range 7–29).

Most of the 75 single-dose patients (64%) received iron sucrose for anaemia in pregnancy; the mean age was 32 years. The average pre-infusion

Hb was 92 g/L with an MCV of 75 fl [Table 1].

Only 2 patients had documented adverse effects of dizziness, headache and mild pruritus not requiring infusion interruption or treatment.

The Hb response to a single 200 mg dose of iron sucrose was 9.2 g/L and 12.5 with a 500 mg dose (P = 0.13). Infusion times were 2 h longer for the higher dose [Table 2]. Only one chart contained a calculation of total iron deficit. Ferritin levels were available on 5 patients and all were below normal.

Ongoing protocol development will consider including routine ferritin measurement and standardising the estimation of total iron deficit by making the modified Ganzoni formula readily available to clinicians [Table 3].[15,16] While computing the iron deficit is ideal, applying the Ganzoni formula to adults (60–100 kg) with a Hb level of 80–100 g/L results in an estimated total iron deficit of 1200–1700 mg [Table 4]. Rapid total replacement with iron isomaltoside can be initiated with a maximal dose of 1000 mg, with Hb reassessment in 1–4 weeks.[9,17,18]

DISCUSSION

The haemoglobin response to a single 200 mg dose of iron sucrose was slightly lower than a 500 mg dose (P = 0.13) but required far less nursing time. In a busy clinical setting, this was a significant practical consideration.

The Hb rise of 9 g/L following a 200 mg infusion is consistent with other studies; a 2013 meta-analysis of 75 iron replacement trials (42 using iron sucrose) found a mean increase of 6.5 g/L with an associated 26% decrease in blood transfusions.[1] The use of a 7–30-day follow-up Hb reassessment is standard in iron replacement studies, as 50% of the response occurs by day 5 and 100% by 21 days.[19]

Our average pre-infusion Hb of 92 g/L is considered a moderate iron deficiency anaemia (severe <80), and intravenous replacement is recommended if <6 weeks from parturition or elective surgery.[20,21] The follow-up Hb value of 102 g/L brings the patient over a common clinical benchmark of >100 g/L but is below the ideal recommended pre-operative Hb level of 130 g/L.[21] The paucity of ferritin measurements indicates that most clinicians in this setting identify iron-deficient anaemia by a Hb under 100 g/L with a microcytic MCV (<80 fl) in high-risk populations (obstetrics and pre-surgery).

There are several considerations in standardising iron replacement therapy. The choice of agents, safety in pregnancy, ability for maximal iron deficit correction in one infusion and cost are all relevant.

All intravenous iron preparations are used off-label during pregnancy and are thought to be safe in pregnancy.[22] Most authors agree that intravenous iron should be avoided in the first trimester, but beyond that there is limited consensus on what agent to use.[13,23] In our setting, iron sucrose was initially chosen due to its common use in pregnancy and its excellent safety record.[24,25] It is generally given every 2 days and one of its limitations is the maximal single dose of 500 mg which we found impractical.[2,12]

Table 1: Gender, age, diagnosis and baseline haematology of Sioux Lookout Meno Ya Win Health Centre patients receiving intravenous iron from 2013-2019 for the treatment of iron deficiency anaemia

	Single infusion (n=74)	All single and multiple infusions (n=129)
Age, mean±SD	32.3±17.1	35.9±19.0
Female, n (%)	70 (93)	115 (89.1)
Indication, n (%)		
Anaemia in pregnancy	48 (64)	66 (51)
Other iron deficiency	25 (36)	60 (47)
Pre-operative anaemia	2 (3)	3 (2)
Baseline Hb	91.9±11.6	90.2±12.5
Initial MCV	74.7±9.24	73.3±9.8

Hb: Haemoglobin, SD: Standard deviation, MCV: Mean corpuscular volume

Table 2: Changes in haemoglobin 7-30-day post-intravenous iron infusion

Dosage (mg)*	n	Time of infusion (h)	Mean±SD			95% CI**
			Baseline Hb	Hb post-infusion (g/L)	Change haemoglobin from baseline (g/L)	
200	37	1	93±10.2	102±12.7	9.2±8.4	7.267, 11.133
500	28	3	92±13.8	105±12.5	12.5±8.6	10.521, 14.479

*Missing data for 10 patients: 9 received 300 mg dose; 1 received 250 mg, **Change from baseline haemoglobin. Hb: Haemoglobin, SD: Standard deviation, CI: Confidence interval

While single iron sucrose appears practical for patients with a Hb in the 90s who need to be nudged over the 100 g/L mark, higher iron replacement requirements require multiple doses/visits. Our study did not analyse the 54 patients with multiple infusions due to the large variety of doses and schedules used by clinicians. This reflects a wide variety of clinical approaches, and perhaps, some confusion and standardising of the replacement of larger iron requirements would be a useful next step.

Of the three intravenous iron preparations presently available in Canada, only iron isomaltoside[26] can deliver a high dose of iron in one infusion [Table 5]. It was introduced in Europe in 2010 where it is used in pregnancy.[27-29] It was approved in Canada for general use in 2018; as the 'new kid on the block', it is not yet widely used in pregnancy here, despite its acknowledged safety profile.[28-32] In Ontario intravenous iron is not covered by the Ontario Drug Benefits Plan, so the patient may be required to cover a cost of $400–500, if the therapy is not covered by the hospital pharmacy. As a hospital expense, this will need to be balanced against the cost of cancelling surgery. In our region travel to the hospital often requires airplane travel if a blood transfusion is required, while iron can be done safely in a patient's home community. Fortunately, the federal NIHB drug formulary covers the cost of both iron isomaltoside (Monofer) and iron sucrose (Venofer) for First Nations patients.[7]

Suggested dosing schedules have been developed. If rapid correction is not needed and the patient has easy access to the hospital (24,000 of 29,000 of our catchment area patients live remotely), repeat iron sucrose infusions are possible. Otherwise, iron isomaltoside[26] is a reasonable choice for more rapid, high dose iron replacement in non-pregnant patients, with a safety and efficacy record similar to iron sucrose.[32]

Table 3: Ganzoni iron deficit (mg) calculation for 80 (kg) adult with haemoglobin 90 (g/L)

Body weight (kg) × (target-actual [Hb g/L]) ×0.24+500	Iron deficit (mg)
80×60 (150-90=60) ×0.24+500	1652

Hb: Haemoglobin

Limitations

Despite a 6-year long audit period, our numbers for this analysis were small. There was insufficient data to analyse the Hb response of the 54 patients receiving multiple intravenous iron infusions for more severe anaemia; their doses and schedules varied greatly. The follow-up Hb measurements were over a 1–4-week period post-infusion, and standardised timing of follow-up testing would have allowed more rigorous analysis.

CONCLUSION

A 200 mg infusion of iron sucrose was practical in treating moderate anaemia. Higher

Table 4: Estimated iron deficit (mg) by weight and haemoglobin level (g/L)

Weight (kg)	Hb 80 g/L	Hb 85	Hb 90	Hb 95	Hb 100
60	1508 (mg)	1436	1364	1292	1220
70	1676	1592	1508	1424	1340
80	1844	1748	1652	1556	1460
90	2012	1904	1796	1688	1580
100	2180	2060	1940	1820	1700

Hb: Haemoglobin

Table 5: Intravenous iron preparations available in Canada, common doses and number of infusions required for 1000 mg iron replacement

Generic name**	Trade name	Cost/mg ($)*	Max single dose (mg)	I.V. infusion duration	Dosing for 1000 mg/number of visits
Iron isomaltoside	Monofer	0.47	1000	30-60 min	1000 mg ×1
Iron sucrose	Venofer	0.40	200-500	1-3 h	500 mg ×2 or 200 mg ×5
Sodium ferric gluconate	Ferrlecit	0.45	125	1 h	125 mg ×8

*Based on manufacturer's listed/wholesale price, **Iron dextran is discontinued in Canada[14]

dose (500 mg) therapy required substantially more nursing time. Further standardisation is required. Non-pregnant patients with larger iron deficits may benefit from the use of iron isomaltoside, which can deliver a higher amount of iron at one time. Documentation of the practices and results from other rural centres would assist our knowledge and understanding of the practical treatment of iron deficiency anaemia.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

REFERENCES

1. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: Systematic review and meta-analysis of randomised clinical trials. BMJ 2013;347:f4822.
2. Lim W, Afif W, Knowles S, Lim G, Lin Y, Mothersill C, *et al.* Canadian expert consensus: Management of hypersensitivity reactions to intravenous iron in adults. Vox Sang 2019;114:363-73.
3. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, *et al.* Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA 2015;314:2062-8.
4. Gómez-Ramírez S, Shander A, Spahn DR, Auerbach M, Liumbruno GM, Vaglio S, *et al.* Prevention and management of acute reactions to intravenous iron in surgical patients. Blood Transfus 2019;17:137-45.
5. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, *et al.* Hypersensitivity reactions to intravenous iron: Guidance for risk minimization and management. Haematologica 2014;99:1671-6.
6. Muñoz M, Gómez-Ramírez S, Besser M, Pavía J, Gomollón F, Liumbruno GM, *et al.* Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus 2017;15:422-37.
7. Health Canada. Non-Insured Health Benefits. Drug Benefit List. Available from: https://www.sac-isc.gc.ca/eng/1572893927371/1572893976394. [Last accessed on 2020 Jan 09].
8. Blaustein D, Schwenk M, Chattopadhyay J, Avram M. Recent experience with high-dose intravenous iron administration. Kidney Int 2006;70:S26-9.
9. Walker R, Cromarty H, Kelly L, St Pierre-Hansen N. Achieving cultural safety in aboriginal health services: Implementation of a cross-cultural safety model in a hospital setting. Divers Health Care 2009;6:11-22.
10. Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, *et al.* International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017;72:233-47.
11. Lin Y. Preoperative Anemia-Screening Clinics. Hematology; 2019. Available from: https://ashpublications.org/hematology/article-abstract/2019/1/570/422637/Preoperative-anemia-screening-clinics. [Last accessed on 2020 Jan 23].
12. Venofer Product Monograph. Available from: https://pdf.hres.ca/dpd_pm/00018889.PDF. [Last accessed on 2020 Jan 09].
13. Pavord S, Myers B, Robinson S, Allard S, Strong J, Oppenheimer C, *et al.* UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2012;156:588-600.
14. Northern Health. Discontinuation of Drug: Iron Dextran 50 mg/mL X 2 mL Injection is Discontinued in Canada. Available from: https://physicians.northernhealth.ca/sites/physicians/files/news/documents/2019/iron-dextran-injection-discontinuation-july-2019.pdf. [Last accessed on 2019 Jan 15].
15. Zeller M, Verhovsek M. Treating iron deficiency. CMAJ 2017;189:E409. Available from: https://www.cmaj.ca/content/cmaj/189/10/E409.full.pdf. [Last accessed on 2020 Jan 08].
16. Baird-Gunning J, Bromley J. Correcting iron deficiency. Aust Prescr 2016;39:193-9.
17. Kalra PA, Bhandari S, Saxena S, Agarwal D, Wirtz G, Kletzmayr J, *et al.* A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis-dependent chronic kidney disease patients with anaemia. Nephrol Dial Transplant 2016;31:646-55.
18. 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;92:286-91.
19. Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron, and erythropoiesis. Blood 2000;96:823-33.
20. World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity VMNIS | Vitamin and Mineral Nutrition Information System WHO/NMH/NHD/MNM/11.1. Available from: https://www.who.int/vmnis/indicators/haemoglobin.pdf. [Last accessed on 2020 Jan 09].
21. Munting K, Klein A. Optimisation of pre-operative anaemia in patients before elective major surgery – Why, who, when and how? Anaesthesia 2019;74 Suppl 1:49-57.
22. Auerbach M, Boccia R. How Should we Treat Pregnant Women with Iron Deficiency? Am Soc Hematol News, October 1, 2018. Available from: https://www.ashclinicalnews.org/bleeding disorders/ treat pregnant women iron deficiency/. [Last accessed on 2021 May 25].
23. Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD003094. doi: 10.1002/14651858.CD003094.pub3. PMID: 21975735.
24. Michon N, Bernier P, Ferreira E. Evaluation of the use of intravenous iron supplements in an obstetrics and gynecology department. J Pharm Technol 2014;30:97-101.
25. Qassim A, Mol BW, Grivell RM, Grzeskowiak LE. Safety and efficacy of intravenous iron polymaltose, iron sucrose and ferric carboxymaltose in pregnancy: A systematic review. Aust N Z J Obstet Gynaecol 2018;58:22-39.
26. Monoferric Product Monograph. Available from: https://www.pfizer.ca/sites/default/files/201810/MONOFERRIC_PM_E_193890_22JUN2018.pdf. [Last accessed on 2020 Jan 09].
27. Cancado R, Munoz M. Iron replacement options: Oral and intravenous formulations. Transfus Altern Transfus Med 2012;12:103-14.
28. Wesstrom J. Iron deficiency anemia during pregnancy is it safe to give intravenous iron isomaltoside? Int J Obstet Gynecol 2018;143:269.
29. Abstracts of the XXXI Annual Scientific Meeting of the British Blood Transfusion Society. October 16-18, 2013. Birmingham, United Kingdom. Transfusion Medicine. 2013 Oct;23 Suppl 2:1-74. doi: 10.1111/tme.12070. PMID: 24176047.
30. Auerbach M, Georgieff MK. Guidelines for iron deficiency in pregnancy: Hope abounds: Commentary to accompany: UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188:814-6.
31. Auerbach M. Commentary: Iron deficiency of pregnancy-A new approach involving intravenous iron. Reprod Health 2018;15:96.
32. Juul SE, Derman RJ, Auerbach M. Perinatal iron deficiency: Implications for mothers and infants. Neonatology 2019;115:269-74.