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Intravenous iron therapy for menorrhagic patients with severe iron-deficiency anaemia: a retrospective cohort study

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Background: Patient blood management plays an increasingly important role in the management of menorrhagia. We have used a dose-standardised protocol for intravenous (IV) iron therapy for menorrhagic patients, without complicated dose calculation or prolonged hospitalisation. This study aims to evaluate the efficacy, safety, and patient acceptability of IV iron therapy followed by oral iron supplement based on a dose-standardised protocol for menorrhagic patients with severe iron-deficiency anaemia.
Methods: We retrospectively reviewed records of haemodynamically stable menorrhagic patients with severe iron-deficiency anaemia (haemoglobin level, 6-8 g/dL) who were admitted to Kwong Wah Hospital between October 2017 and October 2018. The IV iron therapy involved two doses of 200 mg iron (ferric hydroxide sucrose complex, Venofer) followed by oral iron supplement for at least 4 weeks. Outcome measures included haemoglobin (Hb) and ferritin levels and total iron binding capacity before treatment and 4 weeks after the first dose, and resolution of anaemic symptoms.
Results: Of 182 patients counselled with the option of IV iron therapy or blood transfusion, 138 (75.8%) opted for IV iron therapy. 24 of them were excluded. Of the 114 patients included, 52 (45.6%) had uterine fibroids, 23 (20.2%) had adenomyosis, and 39 (34.2%) had dysfunctional uterine bleeding. At 4 weeks after starting treatment, the mean Hb level increased significantly by 3.4 g/dL, the mean ferritin level increased significantly by 34.4 ng/mL, and the total iron binding capacity reduced significantly by 12.7 μmol/L. Before treatment, 103 (90.4%) patients reported anaemic symptoms. At 4 weeks after treatment started, anaemic symptoms had resolved in 102 (99.0%) patients. The increase in Hb level was not correlated with age, body weight, pre-treatment Hb level, or the interval between the two iron doses. One patient reported an adverse reaction with skin rash, which was treated with antihistamine. She had no anaphylaxis and her second dose was withheld.
Conclusion: IV iron therapy based on a dose-standardised protocol followed by oral iron supplement is a cost-effective, safe, well-accepted, and well-tolerated treatment for menorrhagic patients with severe iron-deficiency anaemia.

Keywords: Anemia, iron-deficiency; Iron; Menorrhagia

Introduction

Menorrhagia is estimated to affect 10% to 30% of women in reproductive age and can cause severe iron-deficiency anaemia[1-3]. Women with severe iron-deficiency anaemia secondary to menorrhagia constitute a distinct group from patients with severe iron-deficiency anaemia caused by renal problems or gastrointestinal bleeding, as these women suffer from cyclical blood loss.

Iron supplement is an effective treatment for anaemia. Oral iron supplement is the first-line treatment because it is convenient and relatively inexpensive. However, oral iron supplement has gastrointestinal side-effects[4,5], which may not be tolerated by patients, and thus intravenous (IV) iron therapy is suggested as second-line treatment. In patients with severe iron-deficiency anaemia secondary to general medical conditions, IV iron therapy has been shown to be effective in increasing the haemoglobin (Hb) level by 6.9 g/dL and reducing the need for allogenic blood transfusion[6]. However, IV iron therapy for menorrhagic women has been less studied. IV iron therapy for menorrhagic patients has reported to increase the Hb level by 2-4 g/dL at 4 weeks after treatment[7,8]. However, IV iron therapy may cause adverse drug reactions, especially anaphylaxis. Nonetheless, the second and third generations IV iron, such as iron sucrose, ferric carboxymaltose, and iron isomaltoside, have been associated with very low

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incidence of allergic reaction[7,9], compared with first-generation IV iron therapy that uses an anaphylactic-inducing Dextran conjugate[10,11]. Although proven to be safe, the wider use of IV iron therapy has been limited by the need for administration of multiple doses and/or multiple admissions, as well as complex dose calculation using the Ganzoni formula. Hence, this study aimed to investigate the efficacy, safety, and patient acceptability of IV iron therapy followed by oral iron supplement based on a dose-standardised protocol for menorrhagic patients.

Methods

This retrospective cohort study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (Reference: KC/KE-18-0275/ER-1). Records of haemodynamically stable menorrhagic patients with severe iron-deficiency anaemia (Hb level, 6-8 g/dL) who were admitted to Kwong Wah Hospital between October 2017 and October 2018 were retrieved. Patients were given the choice of blood transfusion or IV iron therapy that involved two doses of 200 mg iron (ferric hydroxide sucrose complex, Venofer) followed by oral iron supplement for at least 4 weeks. In most patients, the second dose was given within 2 weeks of the first dose as day readmission. In patients required longer hospitalisation, the second dose was given 24 hours after the first dose during the same index admission. Patients were excluded if they (1) had vaginal bleeding secondary to malignant pathologies as confirmed by histology, (2) had received blood transfusion in the same index admission, (3) had not completed both doses of IV iron treatment, and/or (4) had incomplete blood tests data.

Table 1. Clinical characteristics of 114 patients

Characteristic	Mean±SD; median (range)
Age, y	44.0±7.9; 46 (16-54)
Body weight, kg	58.3±9.3; 57 (43.6-89.9)
Interval between two intravenous iron doses, d	12.8±4.4; 13 (1-14)
Uterine size, wks	8.0±5.2; 8 (4-26)

Outcome measures included Hb and ferritin levels and total iron binding capacity before treatment and 4 weeks after the first dose, and resolution of anaemic symptoms. Age, body weight, and uterine size were also recorded.

Hb and ferritin levels and total iron binding capacity before and after treatment were compared using the Wilcoxon signed-rank test or the paired-sample t-test as appropriate. Correlation between the increase in Hb level and clinical factors was assessed using one-way analysis of variance. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS (IBM Corp, Armonk [NY], USA).

Results

Of 182 patients with severe iron-deficiency anaemia secondary to menorrhagia, 138 (75.8%) opted for IV iron therapy. 24 of them were excluded according to the exclusion criteria. Of 114 patients included, 52 (45.6%) had uterine fibroids, 23 (20.2%) had adenomyosis, and 39 (34.2%) had dysfunctional uterine bleeding (Table 1). 19 (13.8%) patients had blood transfusion for menorrhagia or other causes prior to the index admission episode.

At 4 weeks after starting treatment, the mean Hb level increased significantly by 3.4 g/dL, the mean ferritin level increased significantly by 34.4 ng/mL, and the total iron binding capacity reduced significantly by 12.7 μmol/L (Table 2). Before treatment, 103 (90.4%) patients reported anaemic symptoms. At 4 weeks after treatment started, anaemic symptoms had resolved in 102 (99.0%) patients.

The increase in Hb level was not correlated with age, body weight, pre-treatment Hb level, or the interval between the two iron doses. One patient reported an adverse reaction with skin rash, which was treated with antihistamine. She had no anaphylaxis and her second dose was withheld.

Discussion

To the best of our knowledge, this is the first local study of IV iron therapy for menorrhagic patients with

Table 2. Haemoglobin and ferritin levels and total iron binding capacity before and after treatment

Blood parameter	Pre-treatment	4 weeks after first dose of intravenous iron therapy	p Value
Mean±SD (median) haemoglobin, g/dL	7.1±0.7 (7.1)	10.5±1.2 (10.8)	<0.001
Mean±SD (median) ferritin, ng/mL	6.8±9.4 (3)	41.2±28.1 (45)	<0.001
Mean±SD (median) total iron binding capacity, μmol/L	75.2±10.6 (76.5)	62.5±9.2 (62)	<0.001

Table 3. Comparing the Ganzoni formula and the dose-standardised protocol in terms of intravenous iron dosage and drug cost in a sample with a body weight of 60 kg, a baseline haemoglobin (Hb) of 7 g/dL, and a treatment goal of Hb of 10.5 g/dL

	Ganzoni formula	Dose-standardised protocol
Intravenous iron dosage	IV iron needed = body weight × (target Hb - actual Hb) × 2.4 + iron store = 60 kg × (10.5-7 g/dL) × 2.4 + 500 mg = 1004 mg	IV iron 400 mg + oral iron supplement
Drug cost (based on Kwong Wah Hospital Pharmacy Prescription)	Venofer = HK$94.2/100 mg elemental iron × 10 = HK$942	Venofer = HK$94.2/100 mg elemental iron × 4 + ferrous sulphate = HK$0.26/tablet (60 mg elemental iron) × 30 days = HK$94.2 × 4 + HK$0.26 × 30 = HK$376.8 + HK$7.8 = HK$384.6

severe iron-deficiency anaemia. The dose-standardised protocol used was effective in raising both Hb and ferritin levels.

Currently there is no universally agreed guideline on calculating the optimal dosage of IV iron therapy. The Ganzoni formula is the most common method and has been reported to achieve an increase in Hb level of up to 4 g/dL 3 to 4 weeks after IV iron therapy in patients with menorrhagia[7,8]. Oral iron supplement is usually not recommended immediately after IV iron therapy because the intestinal epithelium cannot absorb anymore dietary iron, as the systemic iron store is at its full capacity[12,13].

In our dose-standardised protocol, a lower IV iron dose of 400 mg (rather than >1000 mg based on the Ganzoni formula) was given so that the iron store was not fully replenished and could be further replenished with oral iron supplement for at least 4 weeks. The post-treatment rise in Hb level in our patients was comparable to that reported in other studies using a more complicated dose calculation method. In addition, the treatment cost for each patient reduced by almost 60%. An example comparing the Ganzoni formula and the dose-standardised protocol in terms of IV iron dosage and drug cost is shown in Table 3.

There is a potential advantage for IV iron therapy followed by oral iron supplement for menorrhagic patients with severe iron-deficiency anaemia. We hypothesise that the initial IV iron dose quickly replenishes the extremely low iron store and kicks start the erythropoiesis at a faster rate, and then the erythropoiesis process is supported by the continuous oral iron supplement. This may be more cost-effective, as the cost of oral iron supplement is lower than the cost of IV iron therapy, and can avoid unnecessary blood transfusion, but it may not be effective in patients with poor tolerance or compliance to oral iron supplement. Further subgroup analysis is warranted to identify appropriate patients who can benefit from it.

Body weight is a significant independent variable in the Ganzoni formula calculation. Patients with different body weights respond differently in terms of Hb rise[14]. However, body weight was not correlated with Hb rise in the present study. This may be due to the use of oral iron supplement that gradually increased the iron store and Hb level.

The older generation of IV iron therapy may cause anaphylaxis and severe allergic reaction owing to the high molecular weight carbohydrate conjugate[12]. However, the risk of anaphylaxis is extremely low (1:10 000) for the ferric hydroxide sucrose complex (Venofer)[6,11,15]. In the present study, only one patient had mild allergic reaction with skin rash; no patients developed anaphylaxis or other severe adverse drug reactions. The present study confirmed that IV iron therapy with ferric sucrose is a safe treatment for patients with severe iron-deficiency anaemia. In addition, IV iron therapy is a well-accepted alternative to blood transfusion, as most patients chose IV iron therapy rather than blood transfusion. It is also a well-tolerated treatment, as no patient discontinued treatment except for one with mild drug allergy.

Conclusion

IV iron therapy based on a dose-standardised protocol followed by oral iron supplement is a cost-effective, safe, well-accepted, and well-tolerated treatment for menorrhagic patients with severe iron-deficiency anaemia. Further subgroup analysis is warranted to identify appropriate patients for this dose-standardised protocol.

Declaration

The authors have no conflict of interest to disclose.

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