Hong Kong J Gynaecol Obstet Midwifery 2025;25(2):??-?? | https://doi.org/10.12809/hkjgom.25.2.392

Extended follow-up of a single standardised dose of intravenous iron therapy for severe iron-deficiency anaemia in women with heavy menstrual bleeding: a single-centre retrospective study

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Objective: To investigate the extended outcomes of a single standardised dose of intravenous (IV) iron therapy for severe iron-deficiency anaemia in women with heavy menstrual bleeding (HMB).
Methods: Medical records were retrospectively reviewed in women with severe iron-deficiency anaemia (defined as a haemoglobin [Hb] level of 6-8 g/dL) secondary to HMB who received a single dose of 500 mg IV iron isomaltoside, followed by daily oral iron supplement for 10 weeks between January 2020 and June 2021 at Kwong Wah Hospital. Outcome measures included changes in Hb levels at different time points within 1 year and any hypersensitivity event.
Results: In total, 155 women aged 21 to 55 years with a diagnosis of HMB without an identifiable structural cause (n=48), leiomyoma (n=75), adenomyosis (n=31), or endometrial hyperplasia (n=1) were included in the analysis. They received 159 infusions during the study period. The median Hb level was 7.1 g/dL before treatment and increased to 10.9 g/dL at 3 months and 10.7 g/dL at 6 months (p<0.001 for both). At the 1-year follow-up, the median Hb level was 9.8 g/dL among 25 patients (p<0.001) and 11 g/dL among 19 patients who complied with the treatment (p=0.001). Only 15 women had a recurrence of severe anaemia within 1 year. Moreover, 16 women experienced mild (n=13) or moderate (n=3) hypersensitivity to IV iron therapy, which presented as an urticarial rash and shortness of breath, respectively.
Conclusion: IV iron therapy is an integral component of patient blood management among women with iron-deficiency anaemia secondary to HMB, effectively preventing recurrence of severe anaemia and maintaining Hb levels for up to 1 year. This provides a window for clinicians to investigate the underlying gynaecological conditions and to optimise definite treatment.

Keywords: Anemia, iron-deficiency; Iron isomaltoside 1000; Menorrhagia

Introduction

According to the World Health Organization in 2021, 29.9% of non-pregnant women aged 15 to 49 years have anaemia[1]. In Hong Kong, the prevalence of iron-deficiency anaemia is 10.6% among women of reproductive age (15 to 49 years)[2]. Iron-deficiency anaemia is common among gynaecology patients[3], especially those with heavy menstrual bleeding (HMB). Blood transfusion is a treatment option for severe anaemia in women with HMB. However, the supply, cost, and adverse events of blood transfusion raise an interest in alternative treatments[4]. Patient blood management is a patient-centred, multidisciplinary approach to optimise red cell mass and minimise blood loss. Intravenous (IV) iron therapy is an effective and safe treatment for severe iron-deficiency anaemia[5,6], including HMB[7-10]. IV iron increases haemoglobin (Hb) levels more quickly than oral iron supplementation[11]. Short-term effects of IV iron therapy in women with severe anaemia secondary to HMB have been well demonstrated[7-10]. This study aimed to investigate the extended outcomes of a single standardised dose of IV iron therapy for severe iron-deficiency anaemia in women with HMB.

Methods

Medical records were retrospectively reviewed in women with severe iron-deficiency anaemia (defined as a Hb level of <8 g/dL and a ferritin level of <67 pmol/L) secondary to HMB who received a single dose of 500 mg IV iron isomaltoside (regardless of body weight), followed by ferrous sulphate 300 mg (or ferric hydroxide polymaltose complex 100 mg if ferrous sulphate was not tolerated) daily for 10 weeks between January 2020 and June 2021 at Kwong Wah Hospital. Women re-admitted

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for further infusions were recorded as separate sets of data. Patients were excluded if they were aged <18 years, had received a blood transfusion during the same admission, had other concomitant causes for iron-deficiency anaemia, did not complete the full dose of IV iron infusion, or had no post-treatment Hb level recorded.

The treatment protocol was based on a previous study in our unit, which demonstrated short-term effectiveness in women with HMB[7]. Patient compliance to treatment was inquired. Treatment plan was discussed with each patient before treatment. Patients were followed up at 3 and 6 months[12]; subsequent follow-ups were arranged on an individual basis. Outcome measures included changes in Hb levels at different time points within 1 year or until patients became hysterectomised or menopausal, along with any hypersensitivity events. Hypersensitivity reactions were classified into mild, moderate, and severe, according to the Hospital Authority protocol on iron therapy[13,14]. Mild reactions were defined as infusion reactions including itchiness, flushing, urticaria, slight chest tightness, hypertension, and back or joint pains. Moderate reactions were defined as transient cough, nausea, shortness of breath, tachycardia, and hypotension. Severe reactions were defined as anaphylactic reactions including sudden onset and rapid aggravation of symptoms with wheezing or stridor, periorbital oedema, cyanosis, loss of consciousness, and cardiac or respiratory arrest.

Statistical analysis was conducted using SPSS (Windows version 28.0; IBM Corp, Armonk [NY], US). Wilcoxon signed-rank test was used to compare the Hb levels at different time intervals. A p value of <0.05 was considered statistically significant.

Results

Of 207 women with severe iron-deficiency anaemia who received a single standardised IV iron therapy, 52 were excluded owing to blood transfusion during the same admission (n=47) or incomplete IV iron infusion (n=5), whereas two women received three separate infusions during the study period and were counted as six separate sets of data. In total, 155 women (88 Chinese and 67 non-Chinese) aged 21 to 55 (median, 47) years, weighing 40 to 125 (median, 59) kg, with a diagnosis of HMB without an identifiable structural cause (n=48), leiomyoma (n=75), adenomyosis (n=31), or endometrial hyperplasia (n=1) were included in the analysis. They received 159 infusions during the study period, and 123 women were found to comply with treatment.

The median Hb level was 7.1 g/dL before treatment and increased to 10.9 g/dL at 3 months and 10.7 g/dL at 6 months (p<0.001 for both, Table 1). At the 1-year follow-up, the median Hb level was 9.8 g/dL among 25 women (p<0.001) and 11 g/dL among 19 women who complied with the treatment (p=0.001).

Table 1. Increase in haemoglobin (Hb) levels at various time points after intravenous iron therapy

Time	Hb level, g/dL*	Increase in Hb level, g/dL*	p Value
All patients			
Pre-treatment (n=159)	7.1 (6.7-7.6)	-	-
Post-treatment <1 month (n=6)	10.8 (10.4-11.9)	3.4 (2.7-5.3)	0.028
Post-treatment 3 months (n=90)	10.9 (9.5-12.4)	3.7 (2.6-5.3)	<0.001
Post-treatment 6 months (n=119)	10.7 (8.8-12.3)	3.7 (1.6-5.3)	<0.001
Post-treatment 9 months (n=46)	11.0 (9.0-12.5)	3.8 (1.75-5.1)	<0.001
Post-treatment 12 months (n=25)	9.8 (8.7-12.4)	2.7 (1.5-4.7)	<0.001
Patients complied to treatment			
Pre-treatment (n=123)	7.1 (6.7-7.5)	-	-
Post-treatment <1 month (n=5)	10.8 (10.4-12.1)	3.7 (2.6-5.4)	0.043
Post-treatment 3 months (n=70)	10.9 (9.5-12.4)	4.1 (2.6-5.5)	<0.001
Post-treatment 6 months (n=90)	11.0 (9.0-12.3)	3.9 (1.7-5.4)	<0.001
Post-treatment 9 months (n=36)	10.8 (8.3-11.8)	3.8 (1.5-5.0)	<0.001
Post-treatment 12 months (n=19)	11.0 (8.8-12.5)	3.5 (1.6-4.9)	0.001

* Data are presented as median (interquartile range)

Table 2. Change of treatment plan after intravenous iron therapy

Treatment	No. (%) of patients*				
	Heavy menstrual bleeding without identifiable structural cause (n=48)	Leiomyoma (n=75)	Adenomyosis (n=31)	Endometrial hyperplasia (n=1)	Total (n=155)
Non-hormonal treatment	48 (100)	75 (100)	31 (100)	0	154 (99)
Hormones	12 (25)	20 (27)	5 (16)	1 (100)	38 (25)
Long-acting hormones	2 (4)	5 (7)	6 (19)	0	13 (8)
Uterine artery embolisation	0	0	0	0	0
Surgical treatment	0	23 (31)	3 (10)	0	26 (17)

* Patients can have more than one treatment modality

Change of treatment plans was discussed in 136 women. Of the treatment plans for 155 women, 19 were changed to an increased dosage of tranexamic acid, 51 to hormonal treatment, and 26 to surgical treatment (Table 2).

Of the 15 women who had recurrence of severe anaemia and required additional IV iron therapy or blood transfusion, three did not comply with treatment despite counselling, three declined definitive surgical treatment, four relapsed while waiting for surgical management, and five failed the initial treatment and required further treatment. Two women received three separate doses of IV iron therapy within 1 year; they had large leiomyomas and refused either hormonal or surgical treatment.

Moreover, 16 women experienced mild (n=13) or moderate (n=3) hypersensitivity to IV iron therapy, which presented as an urticarial rash and shortness of breath, respectively, during (n=7) or after (n=9) infusion. Additionally, five women had hypersensitivity reactions and stopped IV iron therapy. The rate of hypersensitivity was 13% if these five women were included.

Discussion

Of the 155 women with severe iron-deficiency anaemia secondary to HMB who received a single standardised dose of IV iron therapy followed by oral iron supplement, only 15 had a recurrence of severe anaemia within 1 year. The low recurrence rate is an unexpected finding. Although only 29% and 16% of patients were followed up for Hb levels at 9 and 12 months, respectively, their Hb levels could still be maintained at approximately 10 g/dL. This could be attributed to not only the IV iron therapy but also a review of their treatment plan and their compliance with treatment, both of which help reduce the recurrence rate of severe anaemia after IV iron therapy. Early arrangement for surgical treatment of the underlying causes of HMB for suitable patients is of paramount importance to prevent recurrence of severe anaemia. It is recommended that the waiting time for operations in the public sector be shortened and prescription of a gonadotrophin-releasing hormone analogue be given to induce amenorrhoea and raise Hb levels before surgery[15]. However, owing to the limited resources and constraints on arranging timely surgical slots in public settings, further IV iron therapy for recurrence can buy time before surgical treatment and reduce the more costly blood transfusions.

Patients received oral iron supplementation for 10 weeks immediately after IV iron therapy. There is concern about whether oral iron should be given immediately after IV iron therapy, because of the possible increase in the hepcidin level secondary to high iron load, which can affect oral iron absorption[16-18]. However, such an increase is transient. In patients requiring long-term maintenance secondary to cyclical bleeding, oral iron supplement given immediately after IV iron therapy may help maintain the Hb level among women with HMB.

In our study, no severe hypersensitivity reactions were reported and the rate of hypersensitivity reactions was 13%, which is similar to the 22.7% reported in a US multicentre study in 2016[5,8] and the 8.7% in a UK single-centre study in 2019[19]. Most cases involved mild reactions. This demonstrates that IV iron therapy with iron isomaltoside is safe for women with severe anaemia.

Our study had several limitations. The number of patients with Hb levels measured beyond 6 months was small, because regular blood taking for Hb levels was not included in the departmental protocol for management of HMB. Only 29% and 16% of patients had blood taken at 9 and 12 months, respectively. The patient cohort was heterogeneous, with various underlying causes of HMB. Our findings were confounded by patients' compliance with treatment, dietary modification, and treatment efficacy. Prospective studies on a larger scale and using standardised blood-taking schedules are warranted.

Conclusion

IV iron therapy is an integral component of patient blood management among women with iron-deficiency anaemia secondary to HMB, effectively preventing recurrence of severe anaemia and maintaining Hb levels for up to 1 year. This provides a window for clinicians to investigate the underlying gynaecological conditions and to optimise definite treatment.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have no conflicts of interest to disclose.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analysed during the present study are available from the corresponding author upon reasonable request.

Ethics approval

The present study was approved by the Hong Kong Hospital Authority Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-23-0086/ER-3). All patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided informed consent for all treatments and procedures.

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