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Efficacy and safety of intravenous iron isomaltoside in postpartum anaemia

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Background: Postpartum anaemia adversely affects maternal mood, cognition, and maternal-infant interactions. Intravenous iron isomaltoside is effective and safe for non-pregnant patients with iron deficiency anaemia, but data on its use in Hong Kong women during peripartum period are limited. This study aims to determine the effectiveness and safety of iron isomaltoside (Monofer) in women with postpartum haemorrhage or anaemic symptoms.
Methods: Records of women who received iron isomaltoside (Monofer) when haemoglobin (Hb) level was <7g/dL (or ≥7g/dL when concomitant with anaemic symptoms) irrespective of mode of delivery between April 2018 and March 2021 were reviewed. Primary outcome measures included response to iron isomaltoside treatment (measured by pre- and post-treatment Hb levels), resolution of anaemic symptoms, and the number and types of adverse reactions related to treatment. Secondary outcome measures included associations between patient characteristics and Hb response.
Results: 126 women were included for analysis. Most were nulliparous, delivered vaginally, and had minor postpartum haemorrhage. Most had a baseline Hb level of <10.0 (mean, 7.36) g/dL, but only 53.2% of them had anaemic symptoms. No women experienced serious adverse events. Only four (3.2%) women had mild adverse events of rash (n=3) or pruritis (n=1). At the 6-week follow-up, the mean Hb level increased 4.39 g/dL to 11.8 g/dL (p<0.001), with only one woman reporting anaemic symptoms. 12 (9.5%) of 126 women had some form of haemoglobinopathy (usually thalassemia trait) and had lower Hb levels even before pregnancy. Compared with women with normal Hb pattern, women with haemoglobinopathy had lower post-treatment Hb responses (p=0.001). Hb response was positively associated with delivery blood loss (r=0.188) and negatively associated with baseline Hb level (r= -0.279).
Conclusion: Iron isomaltoside (Monofer) is effective and safe for postpartum anaemia. It enables rapid improvement in Hb level and anaemic symptoms, even for those with haemoglobinopathy.

Keywords: Anemia, iron deficiency; Iron isomaltoside 1000

Background

Iron deficiency anaemia is common among pregnant women worldwide, with a prevalence of 41.8% in various degrees[1]. Anaemia in pregnancy is a risk factor for postpartum anaemia[2], and therefore minimising anaemia before delivery is recommended[3]. However, peripartum blood loss may not be preventable[4], and postpartum anaemia remains common, with a prevalence of 22.3% to 22.7%, even in developed regions[5,6]. Postpartum anaemia adversely affects maternal mood, cognition, behaviour, maternal-infant interactions, and postpartum depression[7].

Parenteral/intravenous and oral iron supplementation can improve anaemic symptoms, maternal-infant bonding, and postpartum depression[8-11]. However, intravenous iron agents are associated with serious adverse drug events and should be used with caution[12]. Nonetheless, the newer agents have an estimated incidence of serious adverse drug events of <1 in 200 000[13,14].

Oral iron supplementation is limited by gastrointestinal adverse effects, with an incidence up to 32%[15]. The rate of absorption is low, as the iron transport system can become saturated[16]. In contrast, intravenous iron supplementation markedly reduces gastrointestinal symptoms and does not require long-term dosing[17], resulting in higher compliance to therapy. It reduces the need for transfusions and hence blood- and transfusion-related risks. Experiences with gynaecology patients in Hong Kong have been encouraging[18,19].

The third-generation intravenous iron formulations such as iron isomaltoside (Monofer) minimise labile iron release and hence toxicity[20] and have more complex shells to diminish adverse reactions[21]. This enables single-dose repletion and reduces the risk of adverse drug events[22]. Iron isomaltoside (Monofer) is appropriate for postpartum women after discharge from the maternity unit[23]. However,

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data on its use during antepartum and postpartum periods are limited.

Methods

This study was approved by the Hong Kong East Cluster Research Ethics Committee (reference: HKECREC-2021-062). A retrospective cross-sectional study was conducted in an obstetrics unit with around 2000 deliveries a year and an estimated prevalence of postpartum anaemia of 23%. Records of women who received iron isomaltoside (Monofer) between April 2018 and March 2021 were reviewed. Those who were lost to follow-up or those who received blood transfusion after having received iron isomaltoside were excluded.

Women complicated by postpartum haemorrhage (blood loss >500 mL) or anaemic symptoms irrespective of mode of delivery were assessed for complete blood count on day 2 post-delivery. Iron isomaltoside was offered when haemoglobin (Hb) level was <7g/dL (or ≥7g/dL when concomitant with anaemic symptoms). Blood transfusion was reserved for those with haemodynamic instability. Dosage was standardised as per hospital pharmacy guideline (500 mg for body weight <50 kg, 1000 mg for body weight ≥50 kg). Hb level was checked 4 weeks later to determine the need for further iron repletion.

Vital signs were charted before iron isomaltoside infusion and every 15 minutes during infusion and an hour afterwards. In addition to self-reporting by patients, nurses regularly enquired about adverse or hypersensitivity reactions. Any suspected reactions were managed in accordance with the international guidance[24]. Anaemic symptoms (shortness of breath, palpitation, fatigue, and weakness) were documented before and after infusion and at 6-week follow-up examination.

Primary outcome measures included response to iron isomaltoside treatment (measured by pre- and post-treatment Hb levels), resolution of anaemic symptoms, and the number and types of adverse reactions related to treatment. Secondary outcome measures included associations between patient characteristics and Hb response.

Statistical analysis was performed using SPSS (Windows version 27; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant. Hb levels and anaemic symptoms before and after treatment were compared using the paired-sample t-test. Continuous variables were analysed using linear regression, and discrete variables were analysed using analysis of variance.

Results

There were 6320 deliveries during the study period. 1454 women were estimated to have any degree of postpartum anaemia. Of 150 women who received iron isomaltoside, 11 were lost to follow-up, 13 received blood transfusion after having received iron isomaltoside (mostly owing to tachycardia or hemodynamic instability), and the remaining 126 were included for analysis. Most patients were of Chinese ethnicity, nulliparous, delivered vaginally, and had minor postpartum haemorrhage (Table 1). 15.9% of women received blood transfusion immediately postpartum owing to postpartum haemorrhage; their post-transfusion Hb levels were taken as the baseline Hb levels. In most women, the baseline Hb level were <10.0 (mean, 7.36) g/dL, but only 53.2% of them had anaemic symptoms such as dizziness, shortness of breath, and palpitations.

No women experienced serious adverse events. Only four (3.2%) women had mild adverse events of rash (n=3) or pruritis (n=1). One woman had generalised rash, which resolved with intravenous hydrocortisone. Two women had localised rashes, which subsided spontaneously or after the use of antihistamines. One woman had facial pruritis, which subsided spontaneously.

At the 6-week follow-up, the mean Hb level increased 4.39g/dL to 11.8 g/dL (p<0.001), with only one woman reporting anaemic symptoms (Table 2). 12 (9.5%) of 126 women had some form of haemoglobinopathy (usually thalassemia trait) and had lower Hb levels even before pregnancy. Compared with women with normal Hb pattern, women with haemoglobinopathy had lower post-treatment Hb responses (p=0.001). Hb response was positively associated with delivery blood loss (r=0.188) and negatively associated with baseline Hb level (r= -0.279).

Discussion

The safety profile of iron isomaltoside (Monofer) is good for non-pregnant individuals, with serious adverse drug event rates of 0.3%[25,26] to 0.9%[27], in line with other contemporary intravenous iron formulations[28]. However, mild reactions (particularly infusion site reactions) are not uncommon[29], with rates of 3.3%[30] to 14%[31]. Likewise, the safety profile of new intravenous iron formulations for pregnant women is also good[32], but mild reactions are also not uncommon. In pregnant women who received iron isomaltoside (Monofer), 4.7% developed mild hypersensitivity, which abated spontaneously, and none

Table 1. Characteristics of 126 women who received iron isomaltoside (Monofer)

Characteristic	Value*	p Value
Age, y	33.0±4.4	0.486
Parity	0.33±0.57	0.354
Mode of delivery		0.379
Normal spontaneous delivery	65 (51.1)	
Instrumental	36 (28.6)	
Caesarean section	25 (19.8)	
Ethnicity		0.194
Chinese	111 (8.1)	
Other Asian	13 (10.3)	
Caucasian	2 (1.6)	
Haemoglobinopathy†	12 (9.5)	0.001 (η=0.281/η^2=0.079)
Body mass index, kg/m^2	22.3±3.1	0.948
Delivery blood loss, mL	650±318	0.035 (r=0.188/R^2=0.027)
Transfusion	20 (15.9)	0.522
Baseline haemoglobin, g/dL	7.36±0.61	0.002 (r= -0.279/R^2=0.078)
Baseline mean corpuscular volume, unit	81.2±12.0	0.059
Anaemic symptoms	67 (53.2)	0.888

* Data are presented as mean±standard deviation or No. (%) of participants
† Alpha thal trait (n=4), beta thal trait (n=6), and others (n=2)

Table 2. Haemoglobin level and anaemic symptoms before and after iron isomaltoside infusion in 126 women

	Baseline	6-week follow-up	Change	p Value
No. (%) of women with anaemic symptoms	67 (53.2)	1 (0.8)	-66 (-52.4)	<0.001
Mean haemoglobin level, g/dL				
All women (n=126)	7.36	11.76	+4.39 (4.22-4.57)	<0.001
Women with normal haemoglobin pattern (n=114)	7.37	11.85	+4.48 (4.30-4.66)	<0.001
Women with haemoglobinopathy (n=12)	7.34	10.88	+3.53 (2.90-4.17)	<0.001

had severe reactions or anaphylaxis[33]. In Danish postpartum women, iron isomaltoside (Monofer) was well tolerated, with a mild adverse drug event rate of 13.3%, mostly related to infusion site[34]. Our findings are in line with those of the literature.

Intravenous iron supplementation is effective for iron deficiency anaemia, with Hb responses of 1.6 to 3.2 g/dL in non-pregnant patients[35]. Similarly, intravenous iron supplementation results in superior and faster Hb responses for women with postpartum anaemia[36-38]. Intravenous iron supplementation can reduce[39] or even prevent[40] blood transfusion in postpartum women. Iron isomaltoside (Monofer) enables faster Hb recovery and reduced fatigue, compared with oral iron supplementation, in women with postpartum haemorrhage[35].

In the present study, 12 (9.5%) women had some form of haemoglobinopathy, consistent with the prevalence of thalassemia in Hong Kong[41]. In women with haemoglobinopathy, although Hb improvement was smaller, their Hb level after treatment (10.88 g/dL) was similar to that in their first trimester (10.56 g/dL). This suggests almost complete correction of their iron deficiency

anaemia. Hb response was associated with delivery blood loss and pre-treatment Hb level but not with the pre-treatment mean corpuscular volume. The normal mean corpuscular volume is likely due to elevated haematocrit level secondary to acute blood loss in postpartum anaemia[42,43].

There are limitations to this study. It lacks a control group of oral iron supplementation, which is the standard treatment. The sample size is relatively small and is from a single centre. The study design is retrospective. Nonetheless, the use of iron isomaltoside (Monofer) and management of adverse reactions are based on standardised protocols. The selection bias is small, as only 7.3% of women were lost to follow-up.

Conclusion

Iron isomaltoside (Monofer) is effective and safe for postpartum anaemia. It enables rapid improvement in Hb level and anaemic symptoms, even for those with haemoglobinopathy.

Contributors

LTLL designed the study. LTLL acquired the data. LTLL analysed the data. LTLL drafted the manuscript. WS critically revised the manuscript for important intellectual content. All 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 disclosed no conflicts of interest.

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Data availability

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

Ethics approval

The study was approved by the Hong Kong East Cluster Research Ethics Committee (reference: HKECREC-2021-062). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

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