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SHORT COMMUNICATION

Retrospective review of effectiveness and safety of intravenous ferric carboxymaltose given to children with iron deficiency anaemia in one UK tertiary centre

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Abstract In the paediatric population, ferric carboxymaltose (FCM) is only licenced for use in children older than 14 years, and the data in younger children remains scarce. We retrospectively reviewed data of all paediatric patients less than 14 years old who had received FCM infusion from August 2011 to June 2015 at the John Radcliffe Hospital (Oxford University Hospitals), UK. The patient demographics, significant medical history, FCM dose, and blood investigations (pre-FCM and post-FCM) were reviewed. Of the 51 children, 41 had inflammatory bowel disease. There were 24 girls and 27 boys, aged 1 to 13 years, mean (SD) weight 28.4 (13.6) kg. Fifteen patients received at least one more course of FCM up to 35 months later. The time interval between pre-FCM and post-FCM investigations was 1 to 8 months. An improved, median (range) rise in blood indices following one FCM infusion was haemoglobin 2.7 (− 2.4 to 7) g/dL, serum iron 6.6 (− 0.6 to 21.1) μmol/L, and transferrin saturation 14 (− 14 to 38)%. No adverse outcomes were documented.

Conclusions: FCM was effective in increasing the key blood indices with no adverse outcomes in children less than 14 years of age, with a range of different conditions, majority with gastrointestinal disorders such as IBD.

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What is Known:
- *Ferric carboxymaltose (FCM) given via the intravenous (IV) route has been used widely in adults for the treatment of iron deficiency anaemia.*
- *Sparse data exists on FCM use in paediatric population, including young children*

What is New:
- *FCM infusion should be considered as a means of iron administration in the paediatric population less than 14 years of age*
- *No adverse outcomes were recorded following FCM in a young paediatric population (less than 14 years of age); the majority of whom had gastrointestinal disorders*

Keywords Intravenous ferric carboxymaltose (FCM) · Iron deficiency anaemia (IDA) · Paediatric · Safety · Efficacy

Abbreviations

ESR	Erythrocyte sedimentation rate
FCM	Ferric carboxymaltose

IBD Inflammatory bowel disease
IV Intravenous
IDA Iron deficiency anaemia

Introduction

Iron is the most common nutritional deficiency worldwide, both in developing and developed countries [1]. Iron deficiency anaemia (IDA) has been associated with poorer neurocognitive development in toddlers [10]. The best preventive measure for IDA would be a balanced and diversified diet with iron-rich foods. Yet, when these measures fail or prove insufficient, oral iron supplements are commonly used in the management of IDA. Unfortunately, side effects such as constipation, abdominal discomfort, and nausea often result in poor compliance to oral supplements. Oral iron also poses challenge in children with gastrointestinal (GI) disorders such as inflammatory bowel disease (IBD), since absorption of oral iron in these children may be hampered by the inflamed intestines. Given the high (40–70%) prevalence of anaemia in children with IBD [3], the parenteral route of iron administration is often considered in this population.

Ferric carboxymaltose (FCM; Ferinject®), given via the intravenous (IV) route, available in Europe since 2007 [12], has been used widely in the adult population for treatment of IDA. In adult patients with IBD, the evidence of safety and efficacy of IV iron has been well established. However, in paediatric population, FCM is only licenced for use in children older than 14 years. Although, some off-label use of FCM is reported in children below 14 years, the results are combined for the entire paediatric group up to 18 years [4, 7, 11]. Data on FCM use in young children (< 14 years) is sparse [9].

We aimed to review a series of paediatric patients < 14 years of age treated with FCM to evaluate its effectiveness and safety profile.

Methods

This was a retrospective case review of all children < 14 years of age who received FCM infusion from August 2011 (time when FCM use began in this specific group of children) to June 2015 (time when the data was abstracted), based on a search of pharmacy records of FCM administration at the John Radcliffe Hospital (Oxford University Hospitals), a tertiary care centre in the United Kingdom (UK). Being an anonymized, retrospective review of medical records, ethical approval was not required for the study as per the hospital policy.

Patient data was retrieved from the hospital database system and manual review of case records. Data collected included patient demographics, significant medical history, FCM dose, and blood investigations (pre-FCM and post-FCM) including full blood count, iron profile (iron, transferrin saturation), and erythrocyte sedimentation rate (ESR). Post-FCM blood investigations were done at least 1 month following the infusion.

Children with confirmed IDA received FCM infusion as per the protocol designed by the paediatric pharmacy team from the Oxford University Hospitals. For the purpose of this study, the diagnosis of IDA was based on physicians' documentation in the case notes. Physicians had diagnosed IDA primarily based on the clinical picture and blood investigations such as haemoglobin level and iron panel. A dose of 15 mg/kg (maximum 20 mg/kg) was used and infused over 30 min intravenously. Children received the infusion as a day procedure in the ambulatory ward on an outpatient basis or opportunistically during their inpatient admission for other reasons. All patients who received FCM were monitored in the ward for at least 4 h post-infusion. During drug administration and until the end of observation, parameters such as oxygen saturation, heart rate, blood pressure, temperature, and any adverse reactions were closely monitored. These parameters and adverse reactions (if any) would be documented by the nurse during the administration.

The data was descriptively summarized.

Results

Fifty-three children (53% male), median age 10.7 years, received 72 FCM infusions during the study period. A pair of siblings with homozygote TMPRSS6 mutation consistent with iron refractory iron deficiency anaemia [5] was excluded. Data of 51 children were analysed—41 had IBD, 5 had severe anaemia due to dietary insufficiency, 1 anaemic child being investigated for intestinal tuberculosis, and 4 on parenteral nutrition were reported to receive IV FCM (Table 1).

The mean iron dose was 677 mg (50 to 1000 mg) per patient. The pre- and post-FCM median (range) haemoglobin was 8.9 (3.7–12.8) g/dL and 12.2 (8.7–14.7) g/dL, respectively. The rise in haemoglobin calculated for the 48 children for whom, both pre and post values were available, was 2.7 (− 2.4 to 7) g/dL. Data for other blood indices is given in Table 1. The pre and post values of iron, transferrin saturation, and haemoglobin for individual patients are presented in Fig. 1. One patient with inflammatory enteritis and one with very early onset IBD did not show improvements in the measured parameters likely due to their underlying disease.

Fifteen patients received at least one more course of FCM up to 35 months later, during the reported period. The mean interval between repeat FCM infusions was 12 months (range 3 weeks to 35 months).

Table 1 Characteristics of patients and pre and post blood indices

Characteristics of patients ($N = 51$)			
Females			24
Males			27
Age at time of the first FCM dose (mean ± SD)[a]			0.16 to 13 (8.82 ± 4.28) years
Children less than 5 years old			13
Weight (mean ± SD)[a] kg			28.4 ± 13.6
Mean ESR pre-FCM (SD, range) mm/h			35.5 (35.78, 1–140)
Patients' disease profile:			
(a) IBD			41
• Crohn's disease			15
• Ulcerative colitis			12
• IBD-unclassified			6
• Very early onset IBD			8
(b) Dependent on parenteral nutrition			4
• Short-bowel syndrome due to gastrochisis and necrotizing enterocolitis			2
• Chronic diarrhoea due to microvillus inclusion disease and inflammatory enteritis			2
(c) Severe anaemia due to dietary iron insufficiency			5
(d) Anaemic patient who was being investigated for intestinal tuberculosis (presented with fever, weight loss, and diarrhoea)			1
Blood indices			
	Pre-FCM[b] [*n*] Median (range)	Post-FCM[b] [*n*] Median (range)	Rise [*n*] Median (range)
Haemoglobin (g/dL)	[$n = 48$] 8.9 (3.7–12.8)	[$n = 51$] 12.2 (8.7–14.7)	[$n = 48$] 2.7 (− 2.4 to 7)
Serum iron (μmol/L)	[$n = 33$] 3.0 (1.1–11.5)	[$n = 37$] 10.6 (2.1–23.7)	[$n = 27$] 6.6 (− 0.6 to 21.1)
Transferrin saturation (%)	[$n = 26$] 4.5 (1–29)	[$n = 35$] 17 (2–45)	[$n = 20$] 14 (− 14 to 38)

[a] The youngest child was 2 months and 5 days old with a weight of 3.6 kg when she received a FCM dose of 54 mg. She was antenatally diagnosed with gastroschisis and underwent surgical repair on day one of life with no bowel resection. Her anaemia was a result of poor nutritional status with difficulty in feeding post-surgery

[b] Time interval between pre-FCM and post-FCM investigations was 1–8 (mean 2.4) months

No early or late adverse reactions were recorded in the case notes during the 4 h of observation. Four IBD patients had flares of their disease at the time of FCM infusion, and 18 patients were given FCM within 1 month from the time of acute diagnosis. Yet, based on records of the case notes, the infusion did not seem to worsen their disease or increase infection-related complication, as there was no documentation of sepsis or bacteraemia.

Discussion

Our study found that children under 14 years of age receiving FCM experienced no adverse outcomes, and the majority experienced an improvement in haemoglobin concentration and iron indices.

Similar observations are also made in previous studies describing the use of FCM in children. A study involving 72 patients in Germany (median [range] age 13.5 years [11 months to 18 years]), all with IBD or other gastrointestinal disorders [7] reported haemoglobin increment of 2.4 g/dL (mean haemoglobin 9.5 g/dL at baseline to 11.9 g/dL within 5–12 weeks post FCM). A more recent study published in 2016 from Texas, USA also showed the improvement in haemoglobin level after FCM infusion in children with IDA [11]. The study included 72 patients (median [range] age 13.7 years [9 months to 18 years]) given 116 FCM infusions. Median pre-infusion and post-infusion haemoglobin values were 9.1 and 12.3 g/dL, respectively (at 4–12 weeks after initial infusion; $n = 53$) [11].

Improvements in haemoglobin and iron indices potentially reduce the requirement for red blood cell transfusions. Adult studies have also shown that quality of life can be independently improved by higher haemoglobin concentrations [8]. IV iron is certainly more effective than oral iron, particularly in the setting of acute or chronic inflammation [2, 8]. It

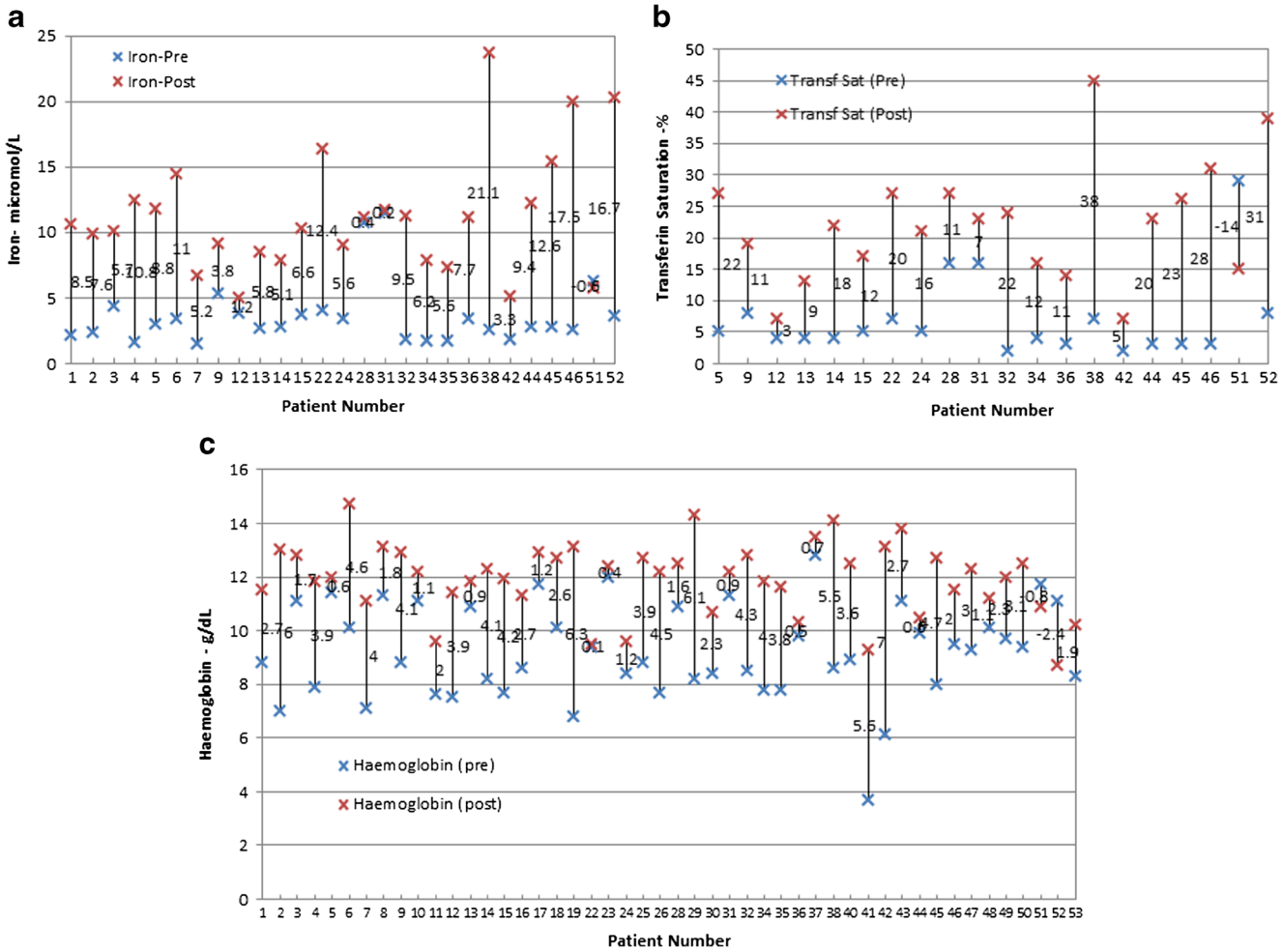

Fig. 1 Pre- and post-values of the **a** iron, **b** transferrin saturation, and **c** haemoglobin

bypasses the effects of hepcidin—an inhibitor of gastrointestinal iron absorption. Some evidence from animal and human studies also suggests that luminal iron exposure may exacerbate intestinal inflammation [6].

Although side effects such as hypersensitive reactions, nausea, dizziness, or headache have been associated with FCM infusions [12], there were none recorded by the medical personnel in this retrospective review.

Of the five, other IV iron preparations available in the European market, FCM is one of the newer IV iron preparations. It can be infused rapidly (15–30 min) and at higher doses (< 1000 mg). This reduces the number of infusions required, making it particularly suitable for ambulatory management as well as time-saving. Thus, although the drug itself may be the most expensive, there may be cost savings in terms of decreased ancillary costs associated with its use.

We acknowledge several limitations of our study, given the retrospective observational nature of it. Repeat blood indices were done during the child's clinical review which could occur between 1 and 8 (mean 2.4) months after the FCM infusion. Hence, improvement in haemoglobin and iron profile could have been compounded by treatment of underlying active disease, improved diet, or oral supplementations which we cannot confirm. The converse is also true; patients could have worsening of their GI disease such as GI blood loss or other comorbidities that can worsen the blood indices during this time period. Unfortunately, limiting the time frame would mean reducing the sample size of the study. We also did not report the mean ferritin level in our study, since this marker is often elevated in acute inflammation. Nonetheless, the blood profile in the majority of children did show improvement following FCM infusion. Additionally, the documentation of adverse events was not done using a specific protocol but was limited to comments recorded in the medical records.

Our study serves to provide insight into the tolerance and effectiveness of FCM in clinical practice. Future, prospective, controlled studies would add more strength to the conclusions that can be drawn about FCM use in children < 14 years.

To our knowledge, this is the first case series reporting the safety and efficacy of FCM usage in a young cohort of

children (under 14 years of age) in the UK with conditions related to GI illnesses and dietary insufficiency. Our data has shown encouraging results and good safety. FCM infusion should be considered as a means of iron administration especially in paediatric patients with GI conditions resulting in IDA, even in younger children.

Conclusions

FCM was effective in increasing key parameters such as haemoglobin, serum iron, and transferrin saturation. There were no adverse outcomes following FCM in the paediatric population < 14 years of age, majority with GI disorders such as IBD.

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Authors' contributions Michelle Li Nien Tan—conception or design of the work, drafting of the manuscript, final approval of version submitted, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Paul-Michael Windscheif—acquisition, analysis, interpretation of data for the work, critical revision, final approval of version submitted, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Being an anonymized, retrospective review of medical records study, ethical approval was not required for the study as per the hospital policy.

Informed consent This study is a retrospective evaluation of the already collected data; thus, formal consent is not required.

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