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Safety and Efficacy of Parenteral Iron in Children with Inflammatory Bowel Disease

Michael Papadopoulos[1], Deepa Patel[2], Roxanna Korologou-Linden[3], Eunice Goto[1], Krishna Soondrum SEM[1], John ME Fell[1] and Jenny Epstein[1]*

[1]Department of Paediatric Gastroenterology, Chelsea and Westminster Hospital, UK

[2]Department of Paediatric Pharmacy, Chelsea and Westminster Hospital, UK

[3]Department of Medicine, St Mary's Campus, Imperial College, UK

Abstract

Objectives: Iron deficiency anemia (IDA) frequently complicates inflammatory bowel disease (IBD) in children and adults. Oral iron may exacerbate gastrointestinal symptoms and absorption may be insufficient in intestinal inflammation. Even where oral iron is successful, repletion of iron stores can be unacceptably slow. Intravenous (IV) iron compounds were in the past associated with serious adverse reactions and historically were considered a last resort in children. New generation preparations have a safer profile in adults although reluctance to use them in children may persist, where safety data is lacking. We investigate the safety and efficacy of ferric carboxymaltose (FCM) and iron sucrose (IS) in children.

Methods: We retrospectively identified all children with IBD who received parenteral iron over a 38 month period in a single regional referral centre. Safety, tolerability and adverse events were established by case note review. Efficacy was assessed by change in hematinic indices pre- and post-treatment.

Results: 47 children (18 male; median age 14yrs, range 3-17) received a total of 104 iron infusions. 44% (21) had Crohn's disease (CD); 56% (27) ulcerative colitis (UC). 40 received FC, eight IS and one both. Three children developed mild rash post infusion which resolved quickly with chlorphenamine. Mean increase in hemoglobin (Hb) was 2.5g/dl (0.3-5.8). Iron levels increased by a mean of 8.4 g/dl (1-25), transfer in saturation by 16.2% (2-47). Transfer in decreased by 0.84 g/dl (0.3-3.4).

Conclusion: New generation parenteral iron preparations are safe, well tolerated and efficacious in children with IDA and IBD.

What is known: Iron deficiency anemia (IDA) is a common complication of inflammatory bowel disease (IBD) and a significant contributor to morbidity.

IDA should be actively treated in IBD.

Parenteral iron is effective and relatively safe in adults.

What is new: The intravenous iron preparations ferric carboxymaltose (FCM) and iron sucrose (IS) are effective treatments for IDA in children with IBD. The safety profiles of FCM and IS are favourable, and similar in children to that in adults.

Keywords: Iron deficiency anemia; Ferric carboxymaltose; Iron sucrose; Intravenous iron; Pediatric

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Introduction

Anemia is one of the commonest extra - intestinal complications of IBD. It is more common in children than adults [1]; affecting an estimated 70% of children with IBD [2]. It occurs more frequently in CD than UC [3]. Anemia in IBD is multifactorial and closely associated with IBD activity. The leading cause is IDA followed by anemia of chronic disease. ID results from gastrointestinal blood loss, poor dietary intake and reduced iron bioavailability. Iron malabsorption is a contributing factor especially in CD affecting the small bowel [4]. Nearly 90% of children with IBD have ID with or without associated anemia [1]. It is increasingly recognized that IDA is a significant contributor to morbidity in IBD. Chronic IDA in children causes fatigue, impairs cognitive development and is

Table 1: Patient demographics, initial haematinics and iron therapy.

Patient	Age/Sex	Disease	Hb (g/dL)	Iron (μmol/L)	Dose (mg)	No of infusions/preparation
1	16F	CD	8.8	3	1500	2 FCM
2	14M	UC	8.2	2	1000	1 FCM
3	15F	CD	8.4	4	900	1 FCM
4	17M	CD	9.4	3	2000	2 FCM
5	16F	CD	9.2	8	1500	2 FCM
6	13F	UC	8.8	2	500	1 FCM
7	15M	UC	8.3	4	1500	2 FCM
8	17M	CD	11.0	8	1000	1 FCM
9	13M	CD	9.2	3	1500	2 FCM
10	14F	UC	10.3	7	1000	1 FCM
11	13M	UC	9.0	3	800	1 FCM
12	13F	CD	7.7	2	800	1 FCM
13	15F	UC	9.1	5	1500	2 FCM
14	13F	CD	11.1	4	1000	1 FCM
15	12M	UC	9.3	3	1500	2 FCM
16	13F	CD	9.6	2	1500	2 FCM
17	16F	CD	8.6	9	1500	2 FCM
18	13F	UC	8.8	6	1500	2 FCM
19	15F	CD	8.9	3	500	1 FCM
20	12F	UC	9.3	3	1500	2 FCM
21	16M	CD	12.1	4	1000	1 FCM
22	12M	UC	9.7	3	1500	2 FCM
23	16F	UC	9.5	3	1000	1 FCM
24	16M	CD	8.9	4	1500	2 FCM
25	15F	UC	8.2	3	1500	2 FCM
26	16F	CD	10.3	3	1000	1 FCM
27	14F	CD	7.5	3	800	1 FCM
28	16F	UC	10.3	4	1000	1 FCM
29	12F	UC	9.8	2	500	1 FCM
30	15M	CD	9.7	2	1500	2 FCM
31	16F	UC	11.6	2	1000	1 FCM
32	14F	CD	10	2	1000	1 FCM
33	16M	CD	9.6	3	3000	2 FCM
34	13M	UC	10	3	850	1 FCM
35	15F	UC	8.6	3	1500	2 FCM
36	16F	CD	10.3	3	930	1 FCM
37	14M	CD	10.4	6	500	1 FCM
38	14F	UC	8.3	unavailable	1500	2 FCM
39	16M	UC	8.8	2	1000	1 FCM
40	13F	UC	8.5	2	1000	1 FCM
41	12M	UC	8.5	2	320	4 IS
42	8M	UC	8.4	3	420	6 IS
16	12F	CD	7.3	2	600	6 IS
43	10F	UC	9.1	3	630	7 IS
44	10F	UC	8.6	2	640	8 IS
45	3M	UC	8.8	1	390	8 IS
46	5F	UC	8.3	2	45	1 IS
47	9M	UC	10.2	5	528	6 IS

Table 2: Haematinic indices pre- and post-treatment. Data were imported into STATA version 14. Descriptive statistics: mean, standard deviation (SD), minimum and maximum were calculated for pre- and post-treatment values of Hb, Tfer saturation, CRP, ESR, transferrin, ferritin and iron. Paired sample Student's T Tests for paired differences were calculated for pre- and post-treatment values for each variable. Hb, transferrin, transferrin saturation, Fe and ESR: p=<0.0001. Ferritin: p=<0.0002. CRP: p=0.94.

		n=	Mean	SD	Min	Max
Index		48	13.52	2.88	3	17
Hb	Pre	48	9.26	1.01	7.3	12.1
	Post	44	11.8	1.28	9.3	15
Tfer saturation	Pre	44	4.66	2.91	1	15
	Post	40	20.95	11.02	3	47
CRP	Pre	20	8.87	15.47	.2	65.0
	Post	19	8.66	12.10	.2	46.0
ESR	Pre	16	37.50	23.67	5.0	112.0
	Post	18	22.06	17.80	2.0	73.0
Transferrin	Pre	42	3.06	0.50	2.3	4.0
	Post	35	2.24	0.42	1.7	4.0
Ferritin	Pre	30	11.3	11.88	2	56
	Post	23	146.43	133.08	10	446
Iron	Pre	47	3.38	1.78	1	9
	Post	40	11.78	5.21	3	25

associated with lower intelligence quotients (IQ), attention deficit and other behavioral disorders [5]. Immune regulation and growth are also negatively impacted [6]. These effects are apparent in ID even in the absence of anemia. Adult IBD patients who are anemic report low quality of life (QOL) indices and there is a marked improvement in QOL when HB is corrected in adults with IBD [7]. For these reasons early recognition and prompt and effective treatment of ID (A) are of paramount importance in IBD care. Oral iron supplementation may be considered first line therapy, although issues with tolerance and adherence to prolonged treatment courses often impair therapeutic success. Blood transfusion as a therapy for IDA carries costs and risks which are well recognized. Newer intravenous (IV) iron preparations with a more favorable side effect profile have become available in the last decade including iron sucrose (IS) and ferric carboxymaltose (FCM) which have been shown to be safe and effective in adults [8-10]. Only a small number of studies on the safety and efficacy of modern IV iron products have been conducted in children. Most of these studied IS not FCM and concerned small numbers of children with chronic kidney disease [11-14]. More recently investigators have shown encouraging safety and efficacy of IS in 24 children with IBD and IDA [15].

Here we describe our 38-month experience of FCM and IS in children with IBD with a focus on safety and efficacy.

Methods

All children with IBD who received IV iron in a single regional referral centre between April 2013 and May 2016 were retrospectively identified via pharmacy records. Inclusion criteria were therefore IBD and IDA. In most cases oral iron was used as first line treatment for IDA. IV iron was used in the following circumstances: (a) patient reported side effects with oral iron; (b) non-resolution of IDA with 3 months of oral iron; (c) physician assessment of severity of either IBD or IDA contraindicates trial of oral iron. Anemia was defined

as HB below reference range for age and gender according to the World Health Organization (WHO) [16]. ID was diagnosed by the combination of low serum iron, low mean red cellular volume (MCV), high transfer in and low iron saturation. Ferritin falls in ID, but rises in the acute phase [17], complicating its interpretation as a marker for IDA in IBD. Ferritin was therefore defined as low in the context of CRP (ferritin <30 if CRP <10 and ferritin <100 if CRP >10). Children with severe atopy or allergies or history of prior anaphylaxis were excluded from the study, and were not offered IV iron therapy. Choice of iron preparation was based primarily on patient age, with those under 12 years of age receiving IS and those over 12 years FCM. Demographic data, disease status, iron preparation type, dose and number of infusions were recorded. Dosage was calculated as a function of body weight and HB, as per manufacturers' recommended dosing schedules. Iron preparations were infused according to British National Formulary guidelines. FCM infusions were administered over 15 to 30 minutes; IS over 50 to 70 minutes. All patients completed a two hour inpatient observation period post infusion during which vital signs were recorded at regular intervals.

Adverse reactions were identified by detailed review of written case notes, nursing observations and nursing, pharmacy and medical electronic records. Efficacy was assessed by pre- treatment and post-treatment iron, transfer in saturation, ferritin, transfer in and HB levels. Change in CRP and ESR were also recorded.

Results

47 children with IBD received 104 IV iron infusions over the study period (Table 1). 29 children were female and 18 male. Mean age was 13.5 years, ranging from 3 to 17 years. 20 had CD (44%) and 27 UC (56%). 40 patients received 58 FCM infusions, average 1.5 infusions per patient. Eight patients received 46 IS infusions; average 5.8 infusions per patient. One patient initially completed a course of IS infusions and 11 months later received FCM as she moved age group (thus total number of infusion episodes studied = 48). The doses ranged from (500 to 1000) mg per infusion for FCM and 70 to 100 mg per infusion for IS. All children over 12 years of age received FCM. Patients under 12 years received IS, which, although also off licence, is in line with greater past pediatric experience and wide spread pediatric practice in the United Kingdom. Choice of iron preparation for children between their 12th and 13th birthdays was made on a case by case basis. Three 12 year olds received FCM and two received IS. Safety. 2/40 patients who received FCM developed rash after completing their first infusion, giving a reaction rate of 5%. Both reactions were mild. In patient 3 rash appeared 30 minutes post infusion, with a small drop in systolic blood pressure which resolved rapidly. The rash resolved after a single dose of IV chlorphenamine with no further complications. Subsequent doses of FCM were not given and the patient continued on oral iron therapy. Patient 10 developed rash one hour post infusion with no systemic compromise. She received a single dose of IV chlorphenamine after which the rash resolved. She did not require a second dose of FCM as adequate increment in HB was achieved with single dose. One patient (case 46) of the eight who received IS developed facial itching and mild eye puffiness 15 minutes into her first infusion, giving a reaction rate of 12.5%. There was no systemic compromise and symptoms resolved with single dose IV chlorphenamine.

Efficacy of the 40 patients who received FCM, 18 received a second dose 1-4 weeks later. Of the 22 children who received single dose, three did not attend for their scheduled second infusion, in one
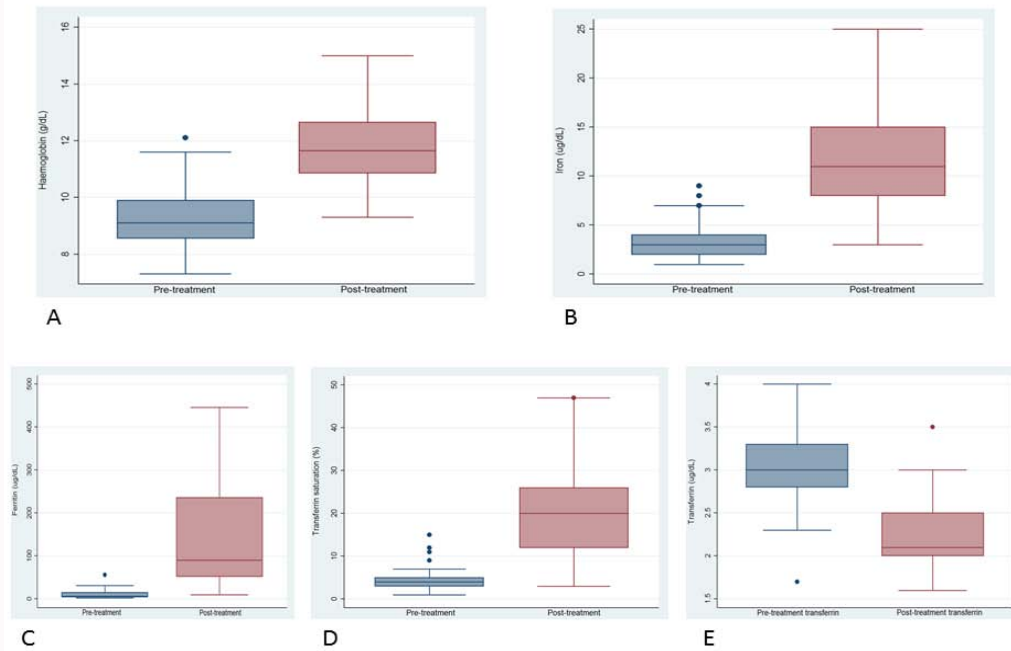
Figure 1: A) Hbpre- and post-treatment (g/dL) (normal ranges(NR) differ with age and sex). p=<0.0001. **B)** Iron pre- and post-treatment (NR 7-27 μg/dL). p=<0.0001. **C)** Ferritin pre- and post-treatment (NR 7-140 μg/dL). p=<0.0002. **D)** Transferrin saturation pre- and post-treatment (NR 16-55%). p=<0.0001. **E)** Transferrin pre- and post-treatment (NR 1.7-3.4 g/L). p=<0.0001.

case the second dose was cancelled because of adverse reaction; one was less than 35 kg –as per administration guidelines and 17 achieved adequate increment in HB with single dose. HB was recorded pre-infusion in all 48 infusion episodes and post-infusion in 44/48 cases. Mean HB pre-infusion was 9.3 (range 7.3 to 12.1) g/dl. Mean HB post treatment was 11.8, an increase of 2.5 per patient (p=<0.0001). There was significant improvement in all hematinic indices following infusion (Table 2) (Figure 1,2).

Discussion

Published evidence strongly supports both proactive treatment of IDA in IBD, and the use of newer IV iron preparations which are efficacious with fewer doses and less allergenic than their predecessors. As in many other areas of pediatric practice, treatment of children has relied upon the extrapolation of adult research. Here we contribute safety and efficacy data for IV iron therapy in pediatric IBD. Oral ferrous supplements are oxidized in the gut, produce activated hydroxyl radicals that affect the mucosa [18] and may provoke gastrointestinal symptoms including bloating, nausea and pain which can be exacerbated in patients with IBD [19]. In inflammatory diseases, iron absorption is reduced and increased hepcidin, an acute phase protein, plays a key role. In health, hepcidin levels rise with total body iron stores and protect against iron overload. Hepcidin is up-regulated in systemic inflammatory states by interleukin (IL) 6 and IL-1, and impairs absorption of oral iron via multiple mechanisms [20]. Adherence to oral iron therapy, particularly in adolescent IBD patients, is frequently suboptimal [21]. Even in the adherent patient, several months of oral supplementation may be required to achieve target HB. The first IV iron introduced in the 1930s, an iron oxyhydroxide complex [22], had major side effects and was only indicated in rare circumstances [23]. In the 1950s a high molecular weight iron dextran (HMW-ID) was developed in which the iron oxyhydroxide complex was surrounded by a shell of dextran polymers [24]. This improved its bioavailability and side effect
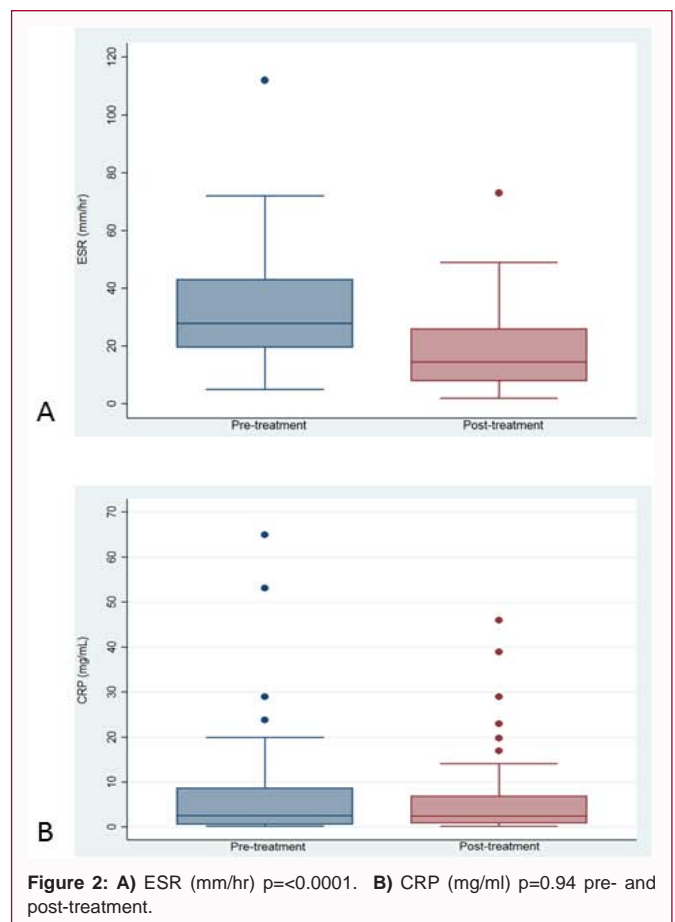

Figure 2: A) ESR (mm/hr) p=<0.0001. **B)** CRP (mg/ml) p=0.94 pre- and post-treatment.

profile, however allergic reactions were frequent [25]. Gradually, low molecular weight dextran compounds became available which caused fewer adverse reactions [26]. Later ferric gluconate (FG)

was introduced and was safer than iron dextran [27]. In 2000 iron sucrose (IS) came into clinical use, whose incidence of anaphylaxis was lower at 0.002%; compared to 0.04% with FG and 0.6-2.3% with HMW-ID [28]. The biggest drawback of IS its low maximum single administrable dose, resulting in multiple separate infusions to reach therapeutic dose. Finally in 2007 ferric carboxymaltose (FCM) became available with a license in Europe for patients above 14 yrs. A single dose of 1000 mg of iron can be given, and administered relatively fast, over 15-60 minutes [29], with no requirement for test dose, thus reducing hospital attendance times and costs. Of the 47 children in our series who received IV iron none experienced major or lasting adverse event. In our series FCM was associated with a 5% mild reaction rate (rash) and IS with a 12.5% mild reaction rate (itch and eye swelling). These numbers do not allow comparative conclusions to be drawn between the two iron preparations in terms of safety, however we provide evidence that parenteral iron and in particular FCM is safe and well tolerated in children. We show that IV iron is a highly efficacious treatment for IDA in children with IBD, inducing clinically and statistically significant increments in HB, Fe and transfer in saturation and reductions in transfer in and ESR. The reduction in ESR was not paralleled by significant reduction in CRP and reflects resolution of IDA rather than change in IBD activity. As well as its lower reported incidence of anaphylaxis, FCM offers a less onerous dosing schedule, no requirement for test dose and shorter infusion time in contrast to IS. In our series we demonstrate safety of FCM in children at least as young as 12 years. This is an off-label use of this medication (<14 years of age). Other investigators have more recently demonstrated safety of FCM in even younger age groups, not specific to IBD [30]. We have selected lower risk cases by excluding those with a personal history of severe allergy, atopy or anaphylaxis to other agents. Whilst the safety profile of parenteral iron in children is probably comparable to that in adults, oral iron remains a safer and less costly option, and should be trialed in the first instance in most cases, where IDA is mild to moderate, IBD activity is quiescent and there is no history of intolerance.

We acknowledge the limitations of this study associated with its retrospective design and heterogeneous clinical nature. Whilst prospective randomized trial design is needed in the field, the current study provides supporting evidence for the safety and efficacy of new generation IV iron preparations in the treatment of IBD-associated IDA in children.

Ethical Review and Approval

The study was approved as a registered clinical audit by the Chelsea and Westminster and West Middlesex University Hospitals Clinical Governance Department reference LA187.

Conflicts of interest and sources of funding: JF is on the advisory board with Janssen and has received travel sponsorship with Falk.

Authorship Statement

MP acquired and interpreted the data and drafted the paper.

DP acquired the data and revised the manuscript.

RKL performed the statistical analyses and revised the manuscript.

EG acquired the data.

KS revised the manuscript.

JF interpreted the data and revised the manuscript.

JE designed the study, interpreted the data and co-wrote the paper.

All authors approved the final version of the manuscript and are accountable for the accuracy and integrity of the work. el sponsorship with Falk.

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