FERRIC CARBOXY MALTOSE IN CORRECTING PREOPERATIVE ANEMIA IN PATIENTS FOR MAJOR ELECTIVE GYNAECOLOGICAL SURGERIES- AN ALTERNATIVE TO BLOOD TRANSFUSION

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LIST OF ABBREVIATIONS

IDA - Iron Deficiency Anaemia.
FCM - Ferric Carboxy Maltose
Hb - Hemoglobin
PCV - Packed Cell Volume
MCV - Mean Corpuscular Volume
MCH – Mean Corpuscular Hemoglobin
MCHC - Mean Corpuscular Hemoglobin Concentration
UV Prolapse - Utero Vaginal Prolapse
DUB - Dysfunctional Uterine Bleeding Pid- Pelvic Inflammatory Disease
MG - Milligram
FL - Femto liters
PG - Pico Grams
GM/DL – Grams Per Deciliters

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INTRODUCTION

Iron deficiency anemia is the most common nutritional deficiency Anemia worldwide. The World Health Organization (WHO) defines irondeficiency anemia (IDA) as hemoglobin (Hb) of less than 12 g/dl in non-pregnant women.[1]

Women are at higher risk of iron deficiency anemia due to blood loss at regular intervals in the form of menstrual loss, pregnancy, and under nutrition. Females are prone to undergo surgeries in their life time due to pregnancy related issues or menstrual problems. Among the women of reproductive age group the incidence of A.B. ranges between 10% and 30%.[2]

Symptoms of iron-deficiency anemia include fatigue, headache, dizziness, breathlessness, palpitations and reduced cognitive function. These symptoms may reduce the patient's health related quality of life (HR-Q.), physical performance and ability to work. Iron-deficiency anemia is associated with co-morbidity and mortality[3]

There are various modalities to treat anaemia oral iron preparation is the most commonly used modality. Oral iron replacement is usually adequate for most patients, but intolerance to oral iron,

Abnormal absorption due to surgery or gastrointestinal disease, significant bleeding, and noncompliance may make oral iron treatment in some patients ineffective Parenteral iron therapy is indicated when there is absolute non-compliance with, or intolerance to, oral iron therapy or proven malabsorption [4]

It circumvents the natural gastrointestinal regulatory mechanisms to deliver non- protein bound iron to the red cells.

Intravenous (IV) iron supplementation was already introduced several decades ago. The first formulations were quite toxic and a test dose was necessary when using the first dextran-containing IV iron preparations because of the risk of anaphylaxis.

Recently, newer IV iron formulations have appeared on the market, which do not contain a requirement for a test dose. For some of these formulations a much higher dose of iron can be delivered as a single administration with acceptable safety and without significant Aes[5]

Ferric carboxymaltose complex is a non-dextran containing IV iron agent designed to be administered in large doses by rapid IV injection.

The ability to safely inject a single dose as large as 1,000 mg in as little as 15 minutes and thereby reduce the need for multiple IV iron infusions renders this novel agent a potentially ideal candidate for the treatment of preoperative anemia.

2

REVIEW OF LITERATURE

In individuals aged >15 years, the WHO considers the threshold hemoglobin concentrations used to define anaemia as 11, 12 and 13g/dL in pregnant women, non- pregnant women and men, respectively[6,3]

Iron deficiency anaemia (IDA) is a common hematological complication with a prevalence of 2% among adult men and 9–20% among adult women depending on race and ethnicity [7]

IDA develops due to an imbalance between iron uptake and requirement, or due to iron loss. In healthy individuals, total body iron levels range from 3 to 4g.[8] 60-70% is present in the blood as circulating iron and the rest (1-1.5 gm) as storage iron. Each gram of haemoglobin contains 3.34gm of iron.

Iron is mostly absorbed from duodenum and upper small intestine in the ferrous state, according to the body needs. The rate of absorption is influenced by a great many factors like iron reserve of the subjects, the presence of inhibitors (e.g., phosphates), and promoters (e.g., ascorbic acid and ascorbic acid rich foods) of iron absorption, and disorders of duodenum and jejunum (e.g., coeliac disease, tropical sprue).

Iron absorption is greater when there is an increased demand for iron as for example during pregnancy. Iron absorption from habitual Indian diets is less than 5 per cent[9], the bioavailability beingpoor.

Iron is necessary for many functions in the body including formation of haemoglobin, brain development and function, regulation of body temperature, muscle activity and catecholamine metabolism. Lack of iron directly affects immune system.

The total daily iron loss of an adult is probably 1 mg and about 12.5 mg per 28 day cycle in menstruating women.[10] Iron is typically absorbed from dietary sources at a rate of 1–2mg/day [8,11.]

Consequently, even the replenishment of iron in patients with “mild” ID can be a slow process[12].

For example, a patient who loses 0 .5 l of blood requires a total of 250mg iron to replace that loss. To put this into a practical context, even if a person absorbed an above average amount of iron from dietary sources (suchas3mg/day, equating to a dietary intake exceeding 10–20 mg/day), it would take 80days to replace such an amount of lost iron.

THREE STAGES OF IRON DEFICIENCY ANAEMIA HAVE BEEN DESCRIBED

A) First stage of iron deficiency have been described without any other detectable abnormalities

B) Intermediate stage of latent iron deficiency that is stores are exhausted, but anaemia has not occurred as yet. Its recognition depends upon measurement of serum ferritin levels. The per cent saturation of transferring falls from normal value of 30 per cent to less than 15 per cent. This stage is the most widely prevalent stage in India.

C) The third stage is that of overt iron deficiency when there is a decrease in concentration of circulating haemoglobin due to impaired haemoglobinsynthesis[13].

The end result of iron deficiency is nutritional anaemia which is not a disease entity. It is rather a syndrome caused by malnutrition in its widest sense[14]

Besides anaemia there may be other functional disturbances such as impaired cell mediated immunity, reduced resistance to infection, increased morbidity and mortality and diminished performance.

The current gold standard for checking for IDA includes looking at both the Hb levels and the serum ferritin values[15]. Ferritin is a protein that stores iron and releases iron as needed; it is the body's regulator against iron deficiency.

By the time a patient is anaemic they have already depleted their iron storage, as evidence by decreased levels of serum ferritin. However ferritin can be falsely elevated because of a secondary inflammatory response.

Although ferritin alone cannot accurately predict IDA, it has been shown to have a possible association with depression and impairment of short- term memory[16,17]

Iron stores are generally considered depleted when ferritin levels are <15mg/L[1] (<100mg/L or higher in patients with chronic disease[18-21] and transferrin saturation is <16%[1,18] (<20% in patients chronic disease) [19-21]

Symptoms of iron-deficiency anaemia include fatigue, headache, dizziness, breathlessness, palpitations and reduced cognitive function[1,3,22].

These symptoms may reduce the patient's health- related quality of life (HR-QOL), physical performance and ability to work[3,23,18].Iron-deficiency anaemia is associated with co- morbidity and mortality.[3,24]

Treatment of iron-deficiency anaemia involves identifying and treating the cause of the condition, as well as replacing iron.1[3,25]

Currently, the standard treatment for anaemia is oral iron supplementation. However, this is limited by patient noncompliance and gastrointestinal symptoms such as nausea, vomiting, and diarrhoea[26].

Absorption of oral iron is influenced by the dosage, the patient's iron storage, and the proximity of taking the medication relative to mealtime. Ideally, the supplement should be taken on an empty stomach as food can impair its absorption[27].

This method of treatment is slow to take effect, often requiring several weeks for results to transpire.

Blood less medicine :

Blood transfusion is like liquid organ transplant. It is a lifesaving procedure but only as volume replacement in conditions of acute blood loss.

There are many adverse events associated with the blood transfusion which overweigh its advantages. Adverse reactions to transfused blood components occur despite multiple tests, inspections, and checks.

The various adverse reactions associated with the blood transfusion are[28]

Reaction	Frequency/ episode : Unit
Febrile (FNHTR)	1–4:100
Allergic	1–4:100
Delayed hemolytic	1:1000
TRALI	1:5000
Acute hemolytic	1:12,000
Fatal hemolytic	1:100,000
Anaphylactic	1:150,000
INFECTIONS	
Hepatitis B	1:220,000
Hepatitis C	1:1,800,000
HIV-1, -2	1:2,300,000
HTLV-I and –II	1:2,993,000
Malaria	1:4,000,000
OTHER COMPLICATIONS	
RBC allosensitization	1:100
HLA allosensitization	1:10
Graft-versus-host disease	Rare

PARENTRAL IRON THERAPY :

Parenteral iron plays a special role in treatment of moderate to severe IDA. They can provide a faster rise in haemoglobin than oral iron and can reduce the need for blood transfusion.

Blood transfusion although an effective and rapid method of iron replenishment, is associated with the risk of transmission of serious illnesses such as HBV, HCV and HIV[29]

In presence of moderate to severe anaemia, there is increase in the endogenous erythropoietin due to tissue hypoxia.

Erythropoietin stimulates development of erythrocyte precursors namely burst forming unit (BFU) and colony forming units (CFU). However, development of mature RBCs is restricted due to lack of iron availability.

With immediate and adequate availability of iron, high erythropoietin levels can accelerate formation of mature erythrocyte by about 4-5 times. This is the probable mechanism by which parenteral iron results in rapid Hb rise especially in severeIDA[30]

Properties of ideal parenteral iron preparation

1 An ideal form of iron for intravenous administration should be capable of delivering sufficient amounts of iron to correct iron deficiency rapidly but without causing any sideeffect.

2 It should be free from any compounds, such as dextran, that could lead to antibody production and/or react with ant-dextran antibodies and induced dextran-induced anaphylacticreaction (DIAR)

3 For ease and comfort of injection, intravenous preparation should have a neutral pH and beisotonic.

4 The final form should withstandsterilization.

Characteristics of an ideal parental iron preparation and comparison with available preparations

	pH	Osmolarity	Antigenicity	Time required for administration	Maximum dose (mg iron)	Half-life	Reduction potential (mV)
Ideal	neutral	isotonic	low	short	high	4–24 h	<–324
Iron sucrose	high	high	low	long (3.5 h for 7 mg Fe/kg b.w.)	500 mg/week	6h	–526
Iron dextran	neutral	isotonic	high (risk of anaphylactic reaction)	long (6 h for 20 mg Fe/kg b.w.)	20 mg Fe/kg b.w.	3–4 days	–475
Ferric carboxymaltose (FCM)	neutral	isotonic	low (does not contain dextran or cross-react with dextran antibodies)	short (15 min for 15 mg Fe/kg b.w.)	1000 mg/week	16h	–390

Iron formulation suitable for intravenous administration need to achieve a balance between effectiveness and safety. Compounds that rapidly release large quantities of ionic forms of iron can cause toxicity, while other iron compound may induce antibody formation and cause serious anaphylactic reactions.

An optimal iron compound for intravenous use should deliver appropriate quantities of iron in a readily available form but should cause minimal side effects and have an excellent safety profile.
The development of such iron compound for intravenous use requires knowledge of the chemical properties as well as of the physiological conditions and ironmetabolism[31]

In order to make a parenteral iron formulation bio available, it has to contain iron (III) oxyhydratecomplexed with another protein or carbohydrate molecule. This prevents release of free iron from the molecule that can cause oxidative damage tobodytissues. This iron complex act like ferreting, the physiological carrier of iron in our body which also contains iron (III) hydroxide at the core of Apo ferritin molecule. Such iron complexes can deliver iron to physiological transport system at neutralpH[32]

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Comparison of various parenteral iron preparations

	Iron dextran	Iron sucrose	SFGC	FCM	Ferumoxytol	Ⅱ-1000
Carbohydrate shell	Dextran (branched polysaccharide)	Sucrose (diasaccharide)	Gluconate (monosaccharide)	Carboxymaltose (branched polysaccharide)	Poluglucose sorbitol carboxymethylether (branched polysaccharide)	Isomaltoside (linear oligopsaccharide)
pH	Neutral	High	Neutral	Neutral	6-8	5-7
Test dose required	Yes	Yes/No	No	No	No	No
Max..infusion dose	up to 20 mg/kg	100-200 mg	62.5-125 mg	1000 mg	510 mg	20 mg/kg
Min.infusion time	360 min	15-30 min	60 min	15 min	Not applicable	30-60 min
Max.injectable single iron dose	100 mg	100-200 mg	125 mg	200 (bolus) - 1000 mg over 15 min	510 mg	100 – 200 mg
Max. IV single injection time	2 min	5-10 min	10 min	Bolus push for 200 mg, 15 min for 1000 mg	17 sec (1ml/sec)	2 to 4 min (50 mg/min)
*Cross-reacts with dextran antibodies**	Yes	No	No	No	Yes	Yes

FERRIC CARBOXYMALTOSE (FCM)

Ferric carboxymaltose is a novel non-dextran iron containing complex which rapidly replenish iron stores, with minimal risks of hypersensitivity and other adverse effects.

CHEMICAL STRUCTURE

Ferric carboxymaltose comprises a macromolecular iron-hydroxide complex of polynuclear iron (III) hydroxide in a carbohydrate shell. The complex has a molecular weight of around 150,000 Daltons. This means that little of the product is lost through renal elimination,

unlike other smaller iron complexes.

CLINICOPHARMACOLOGICAL PROPERTIES PHARMACO KINETICS

Total iron concentrations in the serum increased rapidly after administration of a single dose of intravenous ferric carboxymaltose equivalent to 100–1000mg of iron in the dose-escalation study in 32 patients with iron-deficiency anaemia[33]; dose- dependent, but not quite dose-linear, increases were seen in the maximum serum iron concentration (Cmax) and exposure[33]. Mean Cmax values of 38, 157, 324 and 333mg/mL were achieved mean 0.26, 0.34, 0.99 and 1.21 hours after administration of ferric carboxymaltose equivalent to 100, 500, 800 and 1000mg of iron, respectively[33].

In the corresponding treatment groups, the mean area under the serum iron concentration-time curve was 338, 2365, 5252 and 6415 mgh/mL[33]. The mean volume of distribution of ferric carboxymaltose in the central compartment ranged from 2476 to 3472mL, which corresponds well to the volume of plasma[33,34].

Ferric carboxymaltose is rapidly cleared from the plasma and largely distributed to the bone marrow[34,35]In patients receiving a single dose of ferric carboxymaltose equivalent to 100–1000mg of iron, the mean serum terminal elimination half-life was 7.4–12.3 hours, with a mean clearance of 2.6–4.4mL/min and a mean residence time of 11.2–16.8 hours[33].Negligible renal elimination of iron occurred following administration of ferriccarboxymaltose[33].

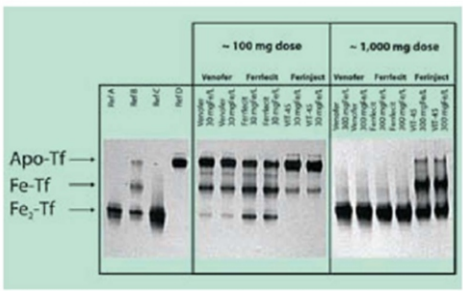
The distribution of ferric carboxymaltose to the bone marrow, liver and spleen has been demonstrated by positron emission tomography[35]. In the study in six patients with anaemia who received a single intravenous 10-minute infusion of 100mg of iron as radiolabelled ferric carboxymaltose35,>80% of radiolabelled ferric carboxymaltose was cleared from the circulation over 8 hours, with the majority distributed to the bone marrow. Indeed, rapid uptake of 52Fe into the bone marrow occurred in the first 10 minutes following ferric carboxymaltose administration with subsequent uptake occurring at a slower, but steady, rate. A distribution phase of 25 minutes was observed for liver and spleenuptake[35].

Ferric carboxymaltose was not removed by high-flux or high-efficiency dialysis membranes to a clinically significant extent during a 4-hour in vitro haemodialysis session[36].

PHARMACODYNAMICS

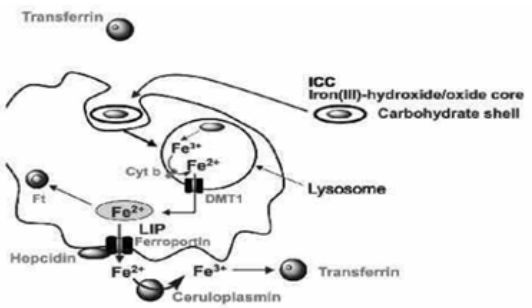
Once in the body, iron is released gradually, avoiding the acute toxicity of many other iron compounds but allowing large amounts of iron to be delivered. This results in a much wider therapeutic window For example, the LD50 (i.e. the dose that kills 50% of experimental mice) is just 11 mg Fe/kg for intravenous administration of the common salt, iron sulphate (FeSO4), around 50 for oligonuclear complexes such as Fe (III) EDTA and Fe (III) gluconate, >200 for iron sucrose, >2500 for iron dextrin and iron dextran[37]. For FCM the LD50 is >1000 mg Fe/kg body weight. Due to the stability of the complex, FCM does not release ionic iron under physiological conditions. The iron hydroxide is tightly bound within a carbohydratecage.

Therefore the iron hydroxide core, with its carbohydrate shell, is taken up by macrophages and enters the lysosomes where Fe3+ can be converted into Fe2+ as required. The Fe2+ is released by a divalent metal transporter (DMT1) then by ferroportin and taken up by transferrin after oxidation by ceruloplasmin.



Following a 1000mg iron dose, iron sucrose and gluconate cause oversaturation of transferrin, while with FCM a balance of Apo transferrin, Fe-Tf and Fe2-Tf is observed. This higher reactivity of iron sucrose and gluconate is reflected in the clinical characteristics and recommended doses, since the maximum single dose for iron gluconate is 62.5-125mg iron that for iron sucrose is 200-500mg iron, while for FCM up to 1000 mg iron can be given in a single dose[38].

Intravenous administration of ferric carboxymaltose results in transient elevations in total iron levels in the serum, ferritin levels and transferrin saturation, and, ultimately, in the correction of haemoglobin levels and replenishment of depleted iron stores[35] Following intravenous injection, macrophages resident in the liver, spleen and bone marrow remove ferric carboxymaltose from the circulating plasma and release iron from the iron-carbohydrate complex[35] The released iron is either taken by ferritin (the main protein responsible for intracellular iron storage in the reticuloendothelial system [RES]) or serum transferrin (the primary protein responsible for iron ion transport from its storage site in the RES to the bone marrow)[39,40,41]. Transferrin binds to transferrin receptors on erythroblasts in the bone marrow. The transferrin receptor/iron-transferrin complex is internalized to provide iron for haemoglobin synthesis and maturation of the redcell[39,41]



Erythroblasts are able to use iron released from ferric carboxymaltose[35].After a single intravenous 10-minute infusion of radiolabelled ferric carboxymaltose equivalent to 100 mg of iron, positron emission tomography showed that a maximum of 61–99% of iron under physiological conditions. The iron hydroxide is tightly bound within a carbohydratecage.

59Fe were utilized by red blood cells after 16–24 days in a study in six patients with iron-deficiency or renal anaemia (baseline haemoglobin

(baseline haemoglobin 10.5–13.2 g/dL) [35]. In the three patients with iron-deficiency anaemia, 91–99% of the radiolabelled iron was utilized after 24 days[40,35].

Intravenous administration of iron preparations has been associated with oxidative stress[41,42]. At therapeutic doses, ferric carboxymaltose should not trigger iron-induced lipid peroxidation in the parenchyma, as iron from ferric carboxymaltose is predominantly deposited in the RES[34]. Tissue damage occurs when transferrin is saturated and non-transferrin-bound iron is taken up in an uncontrolled way by the parenchymal tissues34. Equivalent doses of available intravenous iron preparations (ferric carboxymaltose, HMW iron dextran, LMW iron dextran, sodium ferric gluconate and iron sucrose) differed in their hemodynamic, oxidative stress and inflammatory responses in hearts from normal rats (available as an abstract) [43]. Overall, ferric carboxymaltose and iron sucrose showed a better safety profile with respect to hemodynamic and inflammatory tissue response in heart than the other intravenous iron preparations[43].

The risk of immunological reaction to ferric carboxymaltose in patients who had previously been sensitized to iron dextran appears to be minimal[34] In an in vivo antigenicity study in guinea pigs, ferric carboxymaltose was not associated with cross- reactivity to anti-dextran antibodies[34]

THE RAPEUTIC EFFICACY

The therapeutic efficacy of intravenous ferric carboxymaltose has been evaluated in several randomized, open-label, controlled, multicentre trials in various adult populations with iron-deficiency anaemia (n=200–454 randomized patients), including those with inflammatory bowel disease[44], heavy uterine bleeding[45], postpartum iron deficiency anaemia[26,46,47],or chronic kidney disease not undergoing[48] or undergoing [49]haemodialysis.

In most trials[44-48] the efficacy of ferric carboxymaltose at an iron dose of £1000mg (or 15mg/kg in those weighing <66kg) administered over £15 minutes (subsequent doses administered at 1-week intervals) was compared with that of 6- to 12-week regimens of oral ferrous sulfate

equivalent to 65mg iron three times daily[45,46-48] or 100mg iron twice daily[44,26] Three of these trials[44,26,47]

The primary efficacy endpoints in all trials were related to the effects of treatment on haemoglobin levels (e.g. change from baseline in haemoglobin levels[44,26] or proportion of patients with haematopoietic response45,46-49 . A number of secondary endpoints evaluated other haemoglobin related outcomes, as well as the efficacy of treatment with regard to changes in serum ferritin levels, transferrin saturation and/or HR- QOLoutcomes.

First agent to demonstrate efficacy in chemotherapy associated anaemia

HB LEVEL

Intravenous administration of ferric carboxymaltose was effective in improving haemoglobin levels in trials in many patient populations with iron deficiency anaemia. The various clinical trials in diverse conditions compering ferric carboxymaltose with oral ferrous sulphate shows that treatment with ferric carboxymaltose was significantly ($p<0.05$) more effective than treatment with ferrous sulfate with regard to the secondary endpoint of the change from baseline in haemoglobin levels by study end (week 6[45] or 8[48]) in the trials in patients with non-dialysis dependent chronic kidney disease [48] or heavy uterinebleeding[45]

The proportion of patients with a haematopoietic response to treatment (according to various definitions) was also significantly greater in ferric carboxymaltose than in ferrous sulfate treatment groups in most trial[44-48], at most time points. Ferric carboxymaltose was significantly more effective than ferrous sulfate with regard to the primary endpoints of an in- crease in haemoglobin of >2g /dL at week 6 in the trial in women with heavy uterinebleeding[45], Although ferric carboxymaltose was non inferior, but not superior, to ferrous sulfate withregardtothedifferenceintheprimaryendpointofanincreaseinhaemoglobin>2.0g/dL in the non-inferiority trial in patients with postpartum iron-deficiency anaemia[47], the median time to achieve this endpoint was shorter in ferric carboxymaltose recipients than in

ferrous sulphate recipients (7 vs. 14 days;p<0.001).In another trial in this patient population, the median times to achieve haemoglobin levels >12g/dL or an in- crease in haemoglobin levels of >3.0g/dL were significantly (p< 0.0002) shorter in ferric carboxymaltose recipients than in ferrous sulphate recipients (14 vs 27 days and 15 vs 28 days) [46].

Patients with the most severe anaemia showed the greatest differences in efficacy between ferric carboxymaltose and ferrous sulphate treatment[46,47].

SERUM FERRITIN LEVELS

Intravenous ferric carboxymaltose produced rapid and pronounced increases in serum ferritin levels over the initial treatment period; these levels then declined, but remained higher than baseline[44,26,46-49.]

In recipients of ferric carboxymaltose, baseline serum ferritin levels (5–112mg/L) increased by a mean[26,46-49] or median[44] of »300–600mg/L by week 1[26,46,47] or 2[44,48,49]. These values decreased somewhat in subsequent weeks until the end of the trials (e.g.
»200–400mg/L decrease from peak values by 4 weeks after the final dose[49], week 6[46,47], week 8[48] or week12[44,26]

However, ferritin levels remained »40–400mg/L above baseline levels through to the end of these studies, even though patients usually received their last ferric carboxymaltose infusion during week 2 or 3[44,26,46-49].

The decrease in serum ferritinlevels after the initial few weeks may be due to the utilization of stored iron during the period of increased haemopoiesis that follows administration of ferric carboxymaltose.[34]

In contrast, treatment with ferrous sulfate was associated with only small increases in serum ferritin levels (peak increase »0–50mg/L from baseline of 6.5–105mg/L)[44,26,46-48] Where reported[44,46] the change from baseline in serum ferritin levels was significant at all-time points (p<0.001)[46] or p-value not provided[44] in only the ferric carboxymaltosegroups.

only the ferric carboxymaltosegroups.

Ferric carboxymaltose was associated with a serum ferritin response in significantly (p<0.0002) greater proportions of patients than ferrous sulfate at all-time points44,26

TRANSFERRIN SATURATION

Transferrin saturation improved with intravenous ferric carboxymaltose treatment, with the improvements shown within the first weeks of treatment persisting through to the end of each study. Baseline transferrin saturation (4.0–15.4%) in- creased by a mean [26,46-48] or median[26] of >15–28% by week 2[44,46-48] or 4[26] in ferric carboxymaltose recipients.

The increased rates remained relatively consistent to the end of each study week 6,[46,47] 8[48] or12[44,26] Improvements from baseline in transferrin saturation were significantly (p<0.001) greater with ferric carboxymaltose than with ferrous sulfate at all-time points.

Ferric carboxymaltose was associated with a greater proportion of patients experiencing a transferrin saturation response (defined as transferrin saturation of 20– 50%) than ferrous sulfate at some time points[44,26.] j

HEALTH-RELATED QUALITY OF LIFE

Treatment with intravenous ferric carboxymaltose improved scores on assessments of HR- QOL[44,45,47]. In patients with iron-deficiency anaemia associated with heavy uterine bleeding[45], SF-36 and fatigue analogue scores improved to a significantly greater extent in patients receiving ferric carboxymaltose than in those receiving ferrous sulfate (all p<0.05 at week 2 or later)

TOLERABILITY

In clinical trials, most adverse events associated with ferric carboxymaltose were considered mild to moderate in severity[50,51]

However, the stability of iron sucrose and sodium ferric gluconate is moderate and low, respectively, with corresponding ratings for the risk of acute toxicity of medium and high.

Intravenous infusion of iron preparations has been associated with induction of oxidative stress and the generation of pro- inflammatory substances in animal models, which increases the risk of acute cardiovascular events[23,19,52,53,42,54]

No serious ad verse effects, including deaths, were considered related or likely related to ferric carboxymaltose by the trial investigators

DOSAGE AND ADMINISTRATION

The cumulative dose of ferric carboxymaltose required to restore haemoglobin levels and replete iron stores should be calculated for each patient on an individual basis and should not be exceeded[34] The Ganzoni formula should be used to calculate the required cumulative ferric carboxymaltose dose, where by The cumulative iron deficit [mg] = bodyweight [kg] x (target haemoglobin- actual haemoglobin) [g/dL] x 2.4 + iron storage depot [mg].

In patients weighing <35 and >35 kg, the target haemoglobin should be 13and 15 g/dL, respectively, and the iron storage depot should be 15 mg/kg and 500mg.

Thecalculated cumulative iron dose should be rounded down to the nearest 100mg in patients weighing ≤ 66 kg and up to the nearest 100 mg in those weighing >66 kg[34] Ferric carboxymaltose should be administered intravenously via drip infusion or bolus injection, or administered undiluted directly into the venous limb of the dialyzer during haemodialysis.[34]

Intravenous drip infusions of ferric carboxymaltose may be administered up to a maximum single dose of 1000 mg of iron, but not exceeding 15 mg/kg or the calculated cumulative dose, over a minimum infusion time of up to 15 minutes. Infusions of 1000 mg of iron should not be administered more than per week[34].

COST EFFECTIVENESS

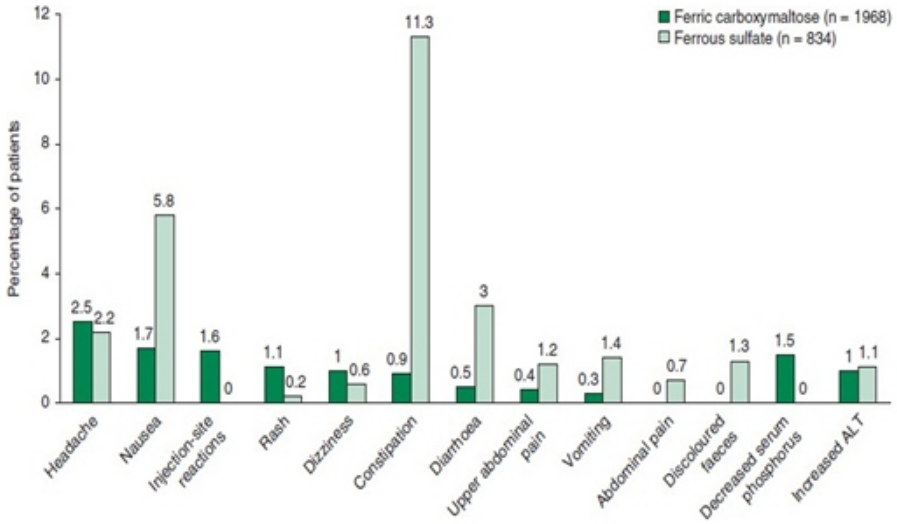
In a multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery.

A cost analysis was performed from a Spanish National Health Service perspective and taking into account both drug acquisition costs (20.07euro per 100 mg for FCM, E11.57 per 100 mg for IS) and i.v. administration costs (time in day hospital, nursing, saline, giving sets, dressing, etc).

For these patient populations, the treatment cost analysis showed that FCM could provide 63 euro savings per treatment compared with IS (95% CI 23.8 – 101.1; P=0.002)[55]

In a randomized, double blind crossover trial comparing single dose Ferric carboxymaltose Vs placebo[50], the adverse events possibly or probably related to treatment that had an incidence numerically higher with ferric carboxymaltose than with placebo included nausea (2.1%vs1.1% of patients),headache(2.0% vs. 1.3%) and dizziness (1.3% vs. 0.2%) during the 24-hour post dose period, and nausea (2.5% vs. 1.1%), headache(2.9% vs. 1.4%), dizziness (1.6% vs 0.2%), rash (1.1% vs 0.2%), increased ALT levels (1.3% vs 0.2%) and increased AST levels (1.3% vs 0%) in the 7-day post-dose period.

The descriptive incidence of possible or probable drug-related adverse events that occurred in ≥1% of patients receiving either ferric carboxymaltose or ferrous sulfate across nine ferrous sulphate controlled trials[51] headache, the most frequently reported adverse event related to ferric carboxymaltose, occurred in <3% of patients in either treatment group51 In general, rash and local injection- site reactions were more common in ferric carboxymaltose recipients.



Ferric carboxymaltose appears to have a low risk of acute toxicity or serious hypersensitivity reactions.[38]

The stability of ferric carboxymaltose, as well as that of LMW iron dextran, is high, providing slow, controlled release of iron, with a corresponding low risk of acute toxicity.[18,38]

3

CONCLUSION

Parenteral iron therapy is emerging as an effective alternative to blood transfusion for correcting iron deficiencyanaemia.In country like India getting safe blood transfusions is difficult due to poor resource setting. In such situation parenteral iron therapy has more importance. The parenteral iron avoids all the major hazards associated with the bloodtransfusion.

The time required to give satisfactory improvement with FCM is fairly short (7 to 21 days) reducing the waiting period for thesurgery.

There is significant improvement in the haematological parameters as well as the clinical signs andsymptoms with FCM.

The cost of the drug appears high but since it's a single time intervention hence it is costeffective.

The patient need not to make multiple hospital visits as happens with the iron sucrose hence it conserves the scares medical resources and also the productive time of thepatient.

Ferric carboxymaltose is an effective and safe drug in correcting anaemia in patients posted for elective major gynaecological surgeries.

4

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