“EFFICACY AND SAFETY OF INTRAVENOUS FERRIC CARBOXY MALTOSE IN IRON DEFICIENCY ANEMIA DURING POST-PARTUM PERIOD”

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ABBREVIATIONS

FCM	:	Ferric Carboxy Maltose
Hb	:	Hemoglobin
WHO	:	World Health Organisation
PCV	:	Packed Cell Volume
FTND	:	Full Term Normal Delivery
GOI	:	Government of India
PPH	:	Postpartum Hemorrhage
IDA	:	Iron Deficiency anemia
RDA	:	Required Dietary Allowance
BMI	:	Body Mass Index
NFHS	:	National Family Health Survey
PG	:	Post Graduation
CDC	:	central Disease Control and Prevention
ACOG	:	American College of Obstetricians and gynecologists
GDP	:	Gross Domestic Product
IV	:	Intravenous
rhEPO	:	Recombinant Human Erythropoietin
SD	:	Standard Deviation

ABSTRACT

OBJECTIVE :

To study efficacy and safety of ferric carboxy maltose (FCM) in postpartum anemia correction.

MATERIALS AND METHODOLOGY:

A prospective observational study done between january to june 2021 at a tertiary health care center, Belagavi, Karnataka. In this study, 90 postpartum women with diagnosis of iron deficiency anemia with hemoglobin ranging between 7 gm% to 11 gm% were included. Women included under study were evaluated for hemoglobin levels, peripheral smear and serum ferritin levels 12 hours after the delivery followed by which injection ferric carboxy maltose (FCM) was given. The drug administration was done under supervision and observed for adverse effects. Women were followed up after three weeks of injection FCM and checked for improvement in hemoglobin levels.

RESULTS :

All women under study were analysed. In the present study common age group was 21 to 24 years. The socio demographic characteristics, obstetric history, vitals, pre-treatment hemoglobin, PCV, Peripheral smear, and ferritin levels was studied. The mean pre-treatment hemoglobin was 9.3 gm/dl. Injection FCM was given according to iron deficit calculated by Ganzoni's formula. There were no serious adverse reactions observed after injection FCM. The mean post treatment was 11.6gm/dl. There was a mean raise of 2.2gm/dl in hemoglobin levels over a period of

three to four weeks after FCM administration. The p value was calculated using students paired t test which was less than 0.0001.

CONCLUSION:

Intravenous FCM is an effective and a safe treatment option for iron deficiency anemia without serious adverse effects.

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INTRODUCTION

Iron (Fe) is abundantly found element in the Earth's crust(1). Since its transition metal, it can accept and donate electrons in redox reactions. This makes it a very crucial element for all basic biological processes. Therefore, from single cellular bacteria to multicellular organism like humans, iron is the most important element for sustenance of life. This metal is known for its important role in several cellular processes such as nucleic acid repair, DNA synthesis, cellular respiration in mitochondria, cell growth and cell death and contributes to host defence mechanism and cellular signalling (2). In addition to these roles, Iron is an important element in haemoglobin (Hb) in the form of Haem and is thus essential for transport of oxygen through red blood cells. Deficiency of iron may lead to decreased iron availability in the body, causes hindrance in erythropoiesis in the bone marrow which results in anaemia.(1)

During pregnancy, iron transfer from maternal to the fetal circulation trough placenta is being regulated by hepcidin molecule which is present in the fetus. Whenever there is low concentration of hepcidin, iron enters blood plasma at a high rate. With higher concentrations of hepcidin, ferroportin is internalized, this leads to trapping of iron in enterocytes, macrophages, and hepatocytes(3,4). Daily intake of iron in the diet is essential and it should be around 1 to 8 mg per day. But, during various physiological process like growth, pregnancy, and lactation the need of external iron requirement also increases. This high demand for iron is essential for the developing fetus and placenta in addition to support mother's haemoglobin levels. Also, pregnant women are prone to loss of iron during and after delivery."(3)

Pregnancy is a state of haemodilution which causes fall in the haemoglobin concentration during the first and second trimesters of normal pregnancies is the most important cause of anaemia. There is a negative iron balance throughout pregnancy, particularly in the latter half, may lead to iron deficiency anaemia during the third trimester. There is a huge demand in iron to meet the requirements of expanding maternal haemoglobin mass and for the fetal growth. As the fetal demand for iron increases, there will be a unidirectional flow of iron to the fetus against a concentration gradient which is regulated by fetal hepcidin; this iron transfer from maternal plasma to fetal circulation is independent of maternal iron stores.

The most common cause of anemia during pregnancy and post-partum period is iron deficiency. The most common manifestation of iron deficiency is drop in haemoglobin concentration. In the third trimester, additional iron is needed for maternal haemoglobin and for transport to the fetus. Since the amount of iron diverted to the fetus is independent of maternal iron stores, the new born infant of a severely anaemic mother does not suffer from iron deficiency anaemia. In early pregnancy, anaemia caused by acute blood loss is common with abruption, ectopic pregnancy and hydatiform mole.

Anaemia is much more common in post-partum from haemorrhage during delivery and poor intake of iron supplementations prior to and during pregnancy. Patients with post-partum anaemia have a increased burden of longer hospital stay, increased risk of puerperal sepsis, need for blood transfusion, and hence incur higher hospital expenses.

Anaemia accounts for a huge global public health burden which is known to affect young children and pregnant women. WHO estimates that the prevalence of anaemia in less than 5 years of age is 42% and 40% of pregnant women worldwide are effected by anaemia. In the seven South and Southeast Asian (SSEA) countries(8), prevalence rate of anaemia is 47% among non-pregnant and 52% in pregnant women.

About 22% of maternal death every year is contributed to anaemia. In asia anaemia is the second largest cause of maternal mortality. Toteja et al: 2006 reported high prevalence of anaemia in India, it is about 84.9% in pregnant women and 90% in adolescent girls in 16 districts of India" (9)

"Postpartum anemia is caused mainly because of poor dietary intake and inadequate iron supplementation prior to and during pregnancy and it is aggravated by peripartum blood loss. According to WHO about 5,29,000 maternal deaths occur every year, where 1,36,000 (25.7%) takes place in India,[1] whereas two-thirds of maternal deaths occur post-partum, PPH being the leading cause of death.WHO defines Iron deficiency anemia as a haemoglobin (Hb) less than 11g/dL (5). The most common cause of anemia in the postpartum period is iron deficiency anemia. Iron deficiency is the most prevalent nutritional deficiency amongst women in reproductive age group.

Iron deficiency during pregnancy and post-partum period may lead to – fatigue, cardio-respiratory problems, increased chances of infection, reduced immunity, lactation failure, increased risk of post-partum haemorrhage, longer hospital stay and hence increased hospital costs and high chances of receiving blood transfusion[(5,7)]

Intravenous iron dextran is known to cause severe life-threatening hypersensitivity reaction, anaphylactoid reactions, arthralgia, myalgia and/or fever, and this demands for the necessity of a test dose and a maximum approved dose is just 100 mg per day. However, with the newer intravenous agents (eg, iron sucrose, ferric gluconate) adverse reactions is markedly lower but requirement of multiple doses and prolonged infusion times make its use restricted. The third generation iv iron formula Ferric Carboxy Maltose (FCM) has the ability to be injected in a single dose as large as 1000mg over 15 minutes and is much safer than the previous iron preparations. In a recently published non-inferiority trial of postpartum iron deficiency anemia found that intravenous ferric carboxy maltose was as effective as oral iron in increasing Hb 2 g/dL or greater”.[5]

FCM is the safer and cost effective choice for treating the post-partum women with iron deficiency anemia with the additional benefits being fewer hospital stay and good compliance.(6) It also has the capacity to improve iron stores for the better outcome of next pregnancy.

OBJECTIVES

The study objectives are:

PRIMARY OBJECTIVE -

To study the efficacy of ferric carboxy Maltose (FCM) in postpartum anemia correction in terms of mean rise in hemoglobin levels after 4 weeks of therapy.

SECONDARY OBJECTIVES -

To study the safety of Ferric Carboxy Maltose (FCM) in terms local and systemic reactions

REVIEW OF LITERATURE

Anemia is defined by WHO as hemoglobin less than 11gm%, which leads to the condition in which the number of red blood cells and their oxygen carrying capacity is insufficient to meet the body's physiological needs. (10)

The word anemia is derived from the Greek word which means an-without and haima-blood. In 19th century "anemia" was used as a clinical Anemia referring to pallor of the skin and mucos membrane. In 1843 Gabriel Andral coined the term that clinical anemia is due to reduced number of red blood cells. Anemia is also described in the ayurvedic literature as 'pandu rog' which mean the disease of pallor.(11)

"The most vulnerable groups for anemia are under five children, adolescent girls, women in reproductive age group, pregnant and lactating women. Anemia can cause adverse health consequences in these vulnerable population which can affect the cognition, productivity and can also lead to morbidity and mortality(12).

The most common cause of anemia world wide is iron deficiency, although other causes like vitamin B12, folate and vitamin A deficiencies, parasitic infection, chronic disease and inherited hemoglobinopathies like thalassemia and sickle cell disease can lead to anemia. Mild anemic patients may be asymptomatic. The most common presentation of anemia include pallor of conjunctiva, palms, skin, glossitis and brittle nails whereas in its severe form of Whereas in its severe form it presents with fatigue, weakness, dizziness and drowsiness."(12)

Anemia and human development:

- 1.9 billion people are affected by anemia globally(13)
- 58.2 million year lived with disability across populations(14)
- Loss of 4% Gross domestic product(GDP) due to anemia globally(15)

- 1 gm/dl increase in hemoglobin level is known to increase in IQ by 1.7 points.(14)

Deaths due to anemia:

- Anemia stands second in the cause of maternal mortality in Asia.
- 22% of the total maternal deaths every year(16)
- 24% of the total perinatal deaths every year(16)
- 90,0000 deaths in both the sexes and all age groups were due to iron deficiency anemia.(17)

Anemia in pregnancy:

Pregnancy is a state of haemodilution which causes fall in the haemoglobin concentration during the first and second trimesters of normal pregnancies is the most important cause of anemia. there is a negative iron balance throughout pregnancy, particularly in the latter half, may lead to iron deficiency anaemia during the third trimester. There is a huge demand in iron to meet the requirements of expanding maternal haemogobin mass and for the fetal growth. As the fetal demand for iron increases, there will be a unidirectional flow of iron to the fetus against a concentration gradient which is regulated by fetal hepcidin; this iron transfer from maternal plasma to fetal circulation is independent of maternal iron stores.

The most common cause of anemia during pregnancy and post-partum period is iron deficiency.

Anemia in post-partum period:

The postpartum period is supposed to be the time of lowest iron deficiency risk because iron status is expected to dramatically improve after delivery(18). Maternal body iron stores are enhanced as the expanded red cell mass of pregnancy contracts at delivery (20).Maternal iron requirements radically decline with the birth of the infant, whose iron needs take precedence over the mother's. Iron losses are significantly reduced by postpartum amenorrhea and the relatively small amount of iron lost through breast milk. Many studies have shown iron status recovering and a concomitant low prevalence of postpartum anemia (19).

Many factors are responsible for low postpartum iron status, which includes maternal characteristics at the start of pregnancy, and events occurring during pregnancy, labour and delivery, and the early postpartum period. Lack of prenatal iron supplementation may increase the risk of postpartum iron deficiency. It is likely that there is a strong relationship between delivery blood loss and risk of postpartum iron deficiency and anemia, but blood loss is difficult to quantify and is therefore lacking in most large datasets (19).

WHO classification of anemia:

- Mild anemia : haemoglobin 10 - 10.9 gm/dl
- Moderate anemia : haemoglobin 7 - 9.9 gm/dl
- Severe anemia : haemoglobin < 7gm/dl

EPIDEMOLOGY

Prevalence

(i) World wide:

- Anemia is the most common global public health burden, affecting around 1.9 billion people around the globe.
- 90% of the anemia cases are from developing country
- Africa and Asia accounts for 85% of anemia cases.(17)

(ii) South east Asia :

- South east Asia has the highest prevalence of anemia across all the age groups in which pregnant women constitutes of about 48.7%.

- Maldives stands first in prevalence (63%) of anemia among women in reproductive age group followed by India (53.1%) among south east Asian countries.
- South east Asia accounts for about half of the global maternal mortality primarily due to anemia(8)

(iii) Indian scenario:

- According to NFHS, 2015-2016, high prevalence of anemia is seen in across all age groups and it's a severe health problem in India.
- In pregnant women its 50% over all and its 52.1% in rural India.
- Among the pregnant women highest prevalence is seen in third trimester.
- In lactating women prevalence is about 57.9%. the high prevalence in lactating women may be due to blood loss during delivery.(26)

(iv) Karnataka:

- Karnataka ranks 13th in anemia Mukt Bharat 2020-21 index and has been tasked with reducing its anemia burden every year by 3%.
- Prevalence among pregnant women is 45% in Karnataka.(27)

Factors associated with increased prevalence of anemia in pregnancy in India:

Anemia is one of the a mjor public health burden in India. Despite of that India was the first developing country to act on anemia prevention by national wide health programmes in terms of distribution of free iron and folic acid supplementations to the pregnant and lactational mother. According to recent fact sheet published by NFHS-4 Information from IIPS and MoHFW (2017) prevalence of anemia (50.3%) in India remains highest in the world. The prevalence of anemia has increased from 52% in NFHS-1 (1992-93) to 53% in NFHS-4 (2015-16) among pregnant women.

In the quest of searching answer for such a high prevalence of anemia in pregnant women in India, the root cause being early marriage and early child bearing age is more prevalent in Indian subcontinent, giving burden of poor pre-pregnant nutritional status and poor health care in Indian women (20).

Nearly about 43% of Indian women who are at present in the age group of 20-24 years are married before 18 years of age, with 22% of women having their first child before the age of 18 years and about 22% before age 20 years(20). Although, there is decline in the incidence of child marriage but it seems to be not satisfactory (from 54% in 1992-1993 to 435 in 2005-2006.(20,21)

Some of the larger states in India like Bihar and Andhra Pradesh the situation is worse, these states have lowest age at marriage and age at first delivery. In the state of Andhra Pradesh which has TFR (1.7 per women) below the replacement level, there is increased prevalence of early marriage and early child birth. The scenario is different in state of Bihar which has high fertility rate, the age of marriage and first child birth is very low.

This trend of early marriage and child birth at very young age will have greater ill effect on women's health and nutritional status which later precipitate women to fall in the greater risk of anemia (21)

Adolescent girls, constitute considerable size of Indian population and are at the greater risk of nutritional deficiency and hence anemia. Adolescence is a period where there is maximum amount of physical, physiological and behavioural changes takes place and hence it makes this age group most vulnerable in development of nutritional deficiencies.(23) There is increased demand for iron among the adolescents for hemoglobin, myoglobin and to compensate the loss occurring due to menstruation and poor dietary habits.(24)

Among the causes of anemia nutritional deficiency leading to iron deficiency is the most common cause. It is the poor dietary habits which is monotonous other than this the intake of phytates in the diet inhibit iron absorption at the intestinal level and hinder the availability of iron in the body. Iron deficiency can also be associated with vitamin a, folic acid, vitamin B12 deficiencies which is quite common in developing countries like India.

Another important cause for anemia is infection. Malaria is affecting 300-500 million people and is the major cause of severe anemia in the endemic areas. Hookworm infestation and schistosomiasis also contribute to the burden of infectious disease causing anemia. About 40 millions of pregnant women are infected with hookworm and about 20 million by schistosomiasis.(25)

Gastrointestinal infection with diarrhoea can also cause anemia because of associated blood loss. Moreover, gastrointestinal infection with diarrhoea can lead to malnutrition which further adds to the cause of anemia. In India, low dietary intake of iron (less than 20mg/day) and folic acid (less than 70 micrograms/day), also intake of food rich in phytates can lead lesser availability of iron in the body and hence precipitate anemia.

In India, many complex socio-cultural factors are involved around the women's overall development. Women are being discriminated right from birth, because of India's inherent patriarchal nature of society girl child is neglected from basic education and nutritional diet. In adolescent phase, when there is maximum requirement of nutritious diet in order to sustain growth and there is about 40ml blood loss every month during menses which leads to 0.6mg of iron loss this increased demand for iron is not met due to social discrimination against women. Women in child bearing age require 2-3 times the amount of iron required by men or women which is not met by the typical Indian diet.

Most of the girl child in rural India are restricted from basic education hence they will be unable to make major decisions in their life it may be about marriage, health or planning a child birth. In some households there is a belief that women should eat last for prosperity and offer whatever best food should be offered to her husband first, hence whatever left out food she consumes is deficient of nutrition values. (25)

Anemia in postpartum women:

Anemia after the delivery of a child (postpartum anemia) is a common problem throughout the world [1, 2]. The prevalence of postpartum anemia is highest in developing countries [30] where it is a major cause of maternal morbidity and mortality [3–5]. It has been estimated that of the ~500,000 maternal deaths occurring each year on a global scale in association with delivery, 20% are caused by peripartum hemorrhage and anemia [3–5]. However, postpartum anemia also constitutes a significant and partly unrecognized problem even in developed countries [6, 7]. In the Western societies, more than 40% of women of reproductive age have small body iron reserves and consequently display an iron status that is not favourable when the women become pregnant. Postpartum anemia is closely connected with the presence of anemia in pregnancy prior to delivery (prepartum anemia) [30], which inevitably will be aggravated after delivery due to the obligatory and sometimes unforeseen blood losses [29]. In the Western countries, the prevalence of prepartum anemia in the third trimester is markedly lower in women who have taken iron supplements during pregnancy compared with non supplemented women [31]. In other words, adequate prevention of iron deficiency and iron deficiency anemia (IDA) during pregnancy also prevents and reduces the prevalence of postpartum anemia. The major causes of postpartum anemia are prepartum iron deficiency/anemia in combination with excessive blood losses at delivery [30]. Normal peripartum blood losses are approximately 250–300 ml, but peripartum hemorrhage of >500 ml occurs in 5%–6% of the women [29,30]. In Europe, in selected series of healthy women after normal delivery, the prevalence of anemia (hemoglobin level <11gm/dl) 1 week postpartum is ~14% in women who have taken iron supplements in pregnancy vs. ~24% in nonsupplemented women [30]. In unselected series of women who have not taken iron supplements, the prevalence of anemia (hemoglobin level <11gm/dL) 48 h after delivery is approximately 50% [29]. In developing countries, the prevalence of postpartum anemia is considerably higher, in the range of 70%–80% . These figures emphasize that postpartum iron deficiency and anemia are continuing major health problems that should be given more attention.(30)

Functional outcomes of iron deficiency anemia in women of child bearing age:

<u>Physical work performance</u>: Iron is found in hemoglobin, myoglobin, oxidative enzymes, and respiratory chain proteins, and is therefore essential for oxidative energy production. All levels of iron deficiency adversely influence tissue oxidative capacity, and severe reductions in hemoglobin causing anemia disturb oxygen carrying capacity .Iron deficiency with and without anemia impair aerobic fitness,(33) endurance capacity, and work efficiency. The impaired physical work capacity and fatigue due to iron deficiency have serious social and economic consequences.(32,33)

Cognitive function and mood : A majority of the research on the relation between iron deficiency and cognition has focused on infants and children, with strong evidence indicating that iron deficient children are at risk of poor cognitive development in the present and future.(34) However, emerging data suggest that iron deficiency adversely impacts the adult brain as well. Distinct from a decrease in hemoglobin synthesis, iron deficiency impacts cognition through a decrease in activity of iron-containing enzymes in the brain. Iron deficiency without anemia has also been associated with higher symptoms of depression and irritability among young women taking oral contraceptives.(19)

Immune function : Iron deficiency inhibit lymphocyte, neutrophil, and macrophage function.(35) Thus, increased susceptibility to infection is a functional consequence of a deficiency of iron, rather than all-cause anemia. Like certain other trace elements, iron deficiency suppresses the immune system to a sufficient extent as to increase risk of morbidity due to viral, microbial, and parasitic infections.(36,37) Improving iron status with adequate intake restores immunocompetence.(37) Nonetheless, a delicate balance in iron requirement exists. Although iron is needed for effective immune response, if the supply of iron is higher than what is required for the host, the invading microbes can use the iron for growth, exacerbating infections. However, the clinical and public health relevance of a high iron supply relative to requirements is not known. (35-37)

Summarizing all together, these data indicate that postpartum iron deficiency has subtle yet insidious effects on economic and social aspects of women’s lives, including the ability to fully engage in childcare, household tasks, and social and leisure activities. Because iron deficiency alters aerobic capacity and endurance, as well as cognition and mood, it has the capacity to diminish productivity associated with both physical and intellectual work.(19)

Evaluation of postpartum anemia:

In the majority of women, postpartum anemia is caused by moderate-to-heavy blood losses in association with delivery [29], which, in turn, may induce acute or subacute anemia, which can be confirmed by measurement of the hemoglobin concentration 12-24 h after delivery. The most commonly used biomarkers of iron status, plasma ferritin and serum soluble transferrin receptor, both appear to be reliable 1 week after delivery [31, 28], while plasma transferrin saturation appears to be an unreliable biomarker several weeks after delivery [31, 38]. From the data available [31], it is suggested that postpartum anemia should be defined as a hemoglobin concentration of less than 11 gm/dl. Whereas peripheral picture may show microcytic hypochromic anemia.

If IDA can be ruled out, further evaluation for anemia should be performed dependent on the history, ethnicity, and region of the world, for example, plasma folate and plasma cobalamin status as well as other vitamin deficiencies and examination for hemolytic anemia, hemoglobinopathy, inflammation, infection, and parasitic infestations. We know that iron deficiency is the most prevalent nutritional deficiency disorder in women of reproductive age. There are, however, major differences in iron nutrition between women from developing and developed countries [31]. In developing regions of the world, prepartum IDA is extremely frequent with a prevalence of more than 50%. In the affluent Western societies, the prevalence is lower, ~25% in women not taking iron supplements [31, 38] and < 5% 0f women taking ferrous iron 40mg or more.

Prevention of postpartum iron deficiency anemia:

In prevention of iron deficiency anemia in postnatal period, iron supplementation and consumption of diet rich in iron is given foremost priority. Least data is available on screening of anemia in post-natal period but most of the studies stress on iron supplementation after delivery. CDC, recommends for screening and iron supplementations for at least 4 to 6 weeks postpartum visits following multiple birth, excessive bleeding during delivery and third trimester anemia. (39)ACOG recommends screening for post partum “when indicated” without outlining the indications.(62)

Recommended dietary allowance (RDA) of iron:

- Non pregnant/non lactating women : 18mg/day
- Pregnant women : 27 mg/day
- Lactating women : 9 mg/day

Clearly, there are major gaps in our knowledge of the best methods of preventing postpartum iron deficiency. Most notably, there are no published data to indicate the effectiveness of the current selective postnatal iron supplementation and anemia screening in preventing postpartum iron deficiency and, more importantly, its functional consequences.(19)

Treatment of postpartum anemia :

<u>Oral iron</u> :

In a women with iron deficient state there will be increased erythropoiesis rate this in turn will accelerate iron absorption in the intestine(42). This state of increased iron absorption makes favourable condition to treat iron deficiency anemia with oral iron in postpartum women.

Many studies suggest that first line of treatment of moderate anemia should be with oral iron. About 100-200mg/day ferrous iron with sustained release formulations can be given between the meals to facilitate absorption at the intestine with lesser side effects(41,43)

The raise in hemoglobin can be documented after 2 weeks of treatment with oral iron. If the hemoglobin raise is more than 10gm/dl it is recommended to continue with oral iron and once it reaches 12mg/dl, iron dose can be reduced to 100mg/day. If the hemoglobin has not reached the target level or its falling after two weeks of treatment with oral iron, then it might be because of noncompliance due to gastrointestinal side effects, inflammatory bowel disease, helicobacter pylori infection or psychological noncompliance. In order to have improved health status and quality of life to its normal during postpartum period i.v. iron therapy should be initiated in such noncompliant patients. If there is successful treatment with oral iron it takes months to replenish body iron stores.(42,43,31)

<u>Intravenous iron</u> :

Ferric iron in i.v. preparations is less tightly bound hence easily available at the plasma level in the body. Second generation i.v. iron preparations include iron dextran and iron sucrose. Ferric carboxymaltose is the newer third generation compound.

Iron deficiency anemia in third trimester is ideally treated with i.v. iron preparations in order to obtain faster rise in hemoglobin levels and faster replenishment of iron stores in the body. The need of postpartum blood transfusions is significantly reduced with the use of i.v. iron during pregnancy.(48) in order obtain appropriate iron reserves in the body with faster rate and lesser side effects i.v. iron therapy is much more superior to oral iron and it stands alternative to the blood transfusion in postpartum iron deficiency (48). About 0.5% people had adverse events following administration of i.v. iron. Before starting of i.v. iron infusion, equipments for cardiopulmonary resuscitation should be made available. Although the third generation i.v. compounds like ferric carboxy maltose and iron isomaltoside have lesser frequency of side effects hen compared to iron sucrose and iron dextran (51).

According to current guidelines, i.v. iron should be given if hemoglobin is less then 9gm/dl. If patient is noncompliant to oral iron or hemoglobin fails to raise even after 2 weeks of oral iron treatment then i.v. iron therapy is recommended.

A total dose of 600 to 1500 mg i.v. iron is sufficient to treat iron deficiency anemia and replenish the iron stores in majority of women. Ganzoni's formula is used to calculate the total dose of iron needed to correct anemia and replenish the iron stores (49,50). Iron sucrose requires repetitive dose of maximum 200mg iron per dose. It requires dilution with 200ml isotonic saline to make it a stable solution before administration and it is administered over 30 min and repeated after 3 days (30). Iron dextran, requires administration of test dose prior to the infusion. About, 500 to 1000mg iron can be given in 500ml saline for about 4 hours.

The newer iron compound, ferric carboxymaltose is approved for the treatment for iron deficiency anemia(49). According to the instructions given by the manufacturers a total 1000mg iron can be dissolved in 250ml normal saline and can be given over 15 to 60 min in a single setting. It is a safer and effective i.v. iron formula compared to the first generation compounds.

Danish manufacturers have introduced latest i.v. iron formula called ferric isomaltoside in 2010. About 1000mg diluted in 100-500ml normal saline can be given in a single set up over 15 to 60 minutes (52).

A medicotechnical report from the Swedish Dental and Pharmaceutical Benefits Agency [53] concluded that “total-dose infusion is cost-effective in patients with iron deficiency who need i.v. iron when at least one extra visit to the clinic can be omitted.” Third-generation i.v. iron preparations have improved the quality of treatment by reducing serious adverse reactions and simplifying the mode of administration. Intravenous iron treatment appears effective in correcting both the anemia and quality-of-life deficits and should be incorporated as a therapeutic option in the management of postpartum IDA. A Norwegian study has evaluated the effect of i.v. iron sucrose vs. oral iron on fatigue in postpartum anemia [54]. The improvements in physical, mental, and total fatigue scores were significantly more pronounced in women treated with i.v. iron than in women taking oral iron [54]. In contrast, the study of Van Wyck et al. [49] did not find any significant difference in fatigue score between women treated with i.v. ferric iron carboxy maltose and oral iron.

Erythropoietin in combination with i.v. iron:

Recombinant human erythropoietin (rhEPO) has been tried to stimulate erythropoiesis and hence obtain faster rate of anemia correction in postpartum women with severe anemia.

Postpartum women who have reduced erythropoiesis because of low endogenous erythropoiesis because of low erythropoietin secretion due to inflammatory disease or infections may be benefited from exogenous administration of rhEPO (46,53).

n the recent studies, it has been learnt that autoantibodies have been developed by some individuals against exogenous as well as endogenous erythropoietin. Hence, rhEPO should be used cautiously and to be administered only in specific indications.

Blood transfusion and plasma expanders :

Patients with uterine bleeding in late pregnancy secondary to any obstetric risk factors like multiple pregnancy, placenta previa, abruption and with severe anemia have high prevalence of postpartum anemia (29). Blood loss during caesarian delivery remains the highest risk factor for anemia in postpartum period(29). Blood loss of more than 1000ml in caesarean is considered as significant and is defined as postpartum haemorrhage, which accounts for about 1.6% of obstetric causes and hence require urgent blood transfusion as a life saving measure.

FERRIC CARBOXY MALTOSE

Ferric carboxymaltose, a novel iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell, allows for controlled delivery of iron to target tissues. Administered intravenously, it is effective in the treatment of iron-deficiency anaemia, delivering a replenishment dose of up to 1000 mg of iron during a minimum administration time of ≤15 minutes. Results of several randomized trials have shown that intravenously administered ferric carboxymaltose rapidly improves haemoglobin levels and replenishes depleted iron stores in various populations of patients with iron-deficiency anaemia, including those with inflammatory bowel disease, heavy uterine bleeding, postpartum irondeficiency anaemia or chronic kidney disease. It was well tolerated in clinical trials. Ferric carboxymaltose is, therefore, an effective option in the treatment of iron-deficiency anaemia in patients for whom oral iron preparations are ineffective or cannot be administered.

Ferric carboxymaltose is a macromolecular ferric hydroxide carbohydrate complex, which allows for controlled delivery of iron within the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins ferritin and transferrin, with minimal risk of release of large amounts of ionic iron in the serum. Intravenous administration of ferric carboxymaltose results in transient elevations in serum iron, serum ferritin and transferrin saturation, and, ultimately, in the correction of haemoglobin levels and replenishment of depleted iron stores.

The total iron concentration in the serum increased rapidly in a dose-dependent manner after intravenous administration of ferric carboxymaltose. Ferric carboxymaltose is rapidly cleared from the circulation and is distributed primarily to the bone marrow (≈80%) and also to the liver and spleen. Repeated weekly administration of ferric carboxymaltose does not result in accumulation of transferrin iron in patients with iron-deficiency anaemia.(62)

PHARMACEUTICAL FORM

Solution for injection/infusion. Dark brown, non-transparent, aqueous solution.

CLINICAL PARTICULARS

1. Therapeutic indications

FCM is indicated for the treatment of iron deficiency when :

– oral iron preparations are ineffective.

– oral iron preparations cannot be used.

– there is a clinical need to deliver iron rapidly.

The diagnosis of iron deficiency must be based on laboratory tests.

2. Posology and method of administration

Monitor carefully patients for signs and symptoms of hypersensitivity reactions during and following each administration of FCM.

FCM should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. The patient should be observed for adverse effects for at least 30 minutes following each FCM administration

<u>Posology</u>

The posology of FCM follows a stepwise approach: [1] determination of the individual iron need, [2] calculation and administration of the iron dose(s), and [3] post-iron repletion assessments. These steps are outlined below:

Step 1: Determination of the iron need

The individual iron need for repletion using FCM is determined based on the patient's body weight and haemoglobin (Hb) level. Refer to Table 1 for determination of the iron need:

Table 1: Determination of the iron need

Hb		**Patient body weight**		
g/Dl	**mmol/L**	**below 35 kg**	**35 kg to <70 kg**	**70 kg and above**
<10	<6.2	500 mg	1,500 mg	2,000 mg
10 to <14	6.2 to <8.7	500 mg	1,000 mg	1,500 mg
≥14	≥8.7	500 mg	500 mg	500 mg

Step 2: Calculation and administration of the maximum individual iron dose(s)

Based on the iron need determined above the appropriate dose(s) of FCM should be administered taking into consideration the following:

A single FCM administration should not exceed:

• 15 mg iron/kg body weight (for administration by intravenous injection) or 20 mg iron/kg body weight (for administration by intravenous infusion)

• 1,000 mg of iron

The maximum recommended cumulative dose of FCM is 1,000 mg of iron per week.

Step 3: Post-iron repletion assessments

Re-assessment should be performed by the clinician based on the individual patient's condition. The Hb level should be re-assessed no earlier than 4 weeks post final FCM administration to allow adequate time for erythropoiesis and iron utilisation.

Special Population – patients with haemodialysis-dependent chronic kidney disease

A single maximum daily dose of 200 mg iron should not be exceeded in haemodialysis-dependent chronic kidney disease patients.

Paediatric population

The use of FCM has not been studied in children, and therefore is not recommended in children under 14 years.

Method of administration

FCM must only be administered by the intravenous route:

• by injection, or

• by infusion, or

• during a haemodialysis session undiluted directly into the venous limb of the dialyser.

FCM must not be administered by the subcutaneous or intramuscular route.

Intravenous injection

FCM may be administered by intravenous injection using undiluted solution. The maximum single dose is 15 mg iron/kg body weight but should not exceed 1,000 mg iron. The administration rates are as shown in Table 2:

Administration rates for intravenous injection of FCM

Volume of FCM required			Equivalent iron dose			Administration rate / Minimum administration time
2	To	4 mL	100	To	200 mg	No minimal prescribed time
>4	To	10 mL	>200	To	500 mg	100 mg iron / min
>10	To	20 mL	>500	To	1,000 mg	15 minutes

Intravenous infusion

FCM may be administered by intravenous infusion, in which case it must be diluted. The maximum single dose is 20 mg iron/kg body weight, but should not exceed 1,000 mg iron.

For infusion, FCM must only be diluted in sterile 0.9% m/V sodium chloride solution as shown in Table below. Note: for stability reasons, FCM should not be diluted to concentrations less than 2 mg iron/ml.

Dilution plan of FCM for intravenous infusion

Volume of FCM required			Equivalent iron dose			Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2	To	4 mL	100	to	200 mg	50 mL	No minimal prescribed time
>4	To	10 mL	>200	to	500 mg	100 mL	6 minutes
>10	To	20 mL	>500	to	1,000 mg	250 mL	15 inutes

3. Contraindications

The use of FCM is contraindicated in cases of:

• hypersensitivity to the active substance, to FCM.

• known serious hypersensitivity to other parenteral iron products.

• anaemia not attributed to iron deficiency, e.g. other microcytic anaemia.

• evidence of iron overload or disturbances in the utilisation of iron.

4. Special warnings and precautions for use

Hypersensitivity reactions

Parenterally administered iron preparations can cause hypersensitivity reactions including serious and potentially fatal anaphylactic/anaphylactoid reactions. Hypersensitivity reactions have also been reported after previously uneventful doses of parenteral iron complexes. There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction).

The risk is enhanced for patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy.

There is also an increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis).

FCM should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available, in an environment where full resuscitation facilities can be assured. Each patient should be observed for adverse effects for at least 30 minutes following each FCM administration. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardio respiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate.

Hypophosphataemic osteomalacia

Symptomatic hypophosphataemia leading to osteomalacia and fractures requiring clinical intervention including surgery has been reported in the post marketing setting. Patients should be asked to seek medical advice if they experience worsening fatigue with myalgias or bone pain.Serum phosphate should be monitored in patients who receive multiple administrations at higher doses or long-term treatment, and those with existing risk factors for hypophosphataemia. In case of persisting hypophosphataemia, treatment with ferric carboxymaltose should be re-evaluated.

Hepatic or renal impairment

In patients with liver dysfunction, parenteral iron should only be administered after careful benefit/risk assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT). Careful monitoring of iron status is recommended to avoid iron overload.

No safety data on haemodialysis-dependent chronic kidney disease patients receiving single doses of more than 200 mg iron are available.

Infection

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the treatment with FCM is stopped in patients with ongoing bacteraemia. Therefore, in patients with chronic infection a benefit/risk evaluation has to be performed, taking into account the suppression of erythropoiesis.

Extravasation

Caution should be exercised to avoid paravenous leakage when administering FCM. Paravenous leakage of FCM at the administration site may lead to irritation of the skin and potentially long lasting brown discolouration at the site of administration. In case of paravenous leakage, the administration of FCM must be stopped immediately.

Excipients

One mL of undiluted FCM contains up to 5.5 mg (0.24 mmol) of sodium. This has to be taken into account in patients on a sodium-controlled diet.

Paediatric population

The use of FCM has not been studied in children.

5. Interaction with other medicinal products and other forms of interaction

The absorption of oral iron is reduced when administered concomitantly with parenteral iron preparations. Therefore, if required, oral iron therapy should not be started for at least 5 days after the last administration of FCM.

6. Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of FCM in pregnant women. A careful benefit/risk evaluation is required before use during pregnancy and FCM should not be used during pregnancy unless clearly necessary.

Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with FCM should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

Foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women.

Animal data suggest that iron released from FCM can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus.

Breast-feeding

Clinical studies showed that transfer of iron from FCM to human milk was negligible (≤1%). Based on limited data on breast-feeding women it is unlikely that FCM represents a risk to the breast-fed child.

Fertility

There are no data on the effect of FCM on human fertility. Fertility was unaffected following FCM treatment in animal studies.

7. Effects on ability to drive and use machines

F is unlikely to impair the ability to drive and use machines.

8. Undesirable effects

Adverse drug reactions (ADRs) reported during clinical studies in which >8,000 subjects received Ferinject, as well as those reported from the post-marketing experience (see table footnotes for details).

The most commonly reported ADR is nausea (occurring in 2.9% of the subjects), followed by injection/infusion site reactions, hypophosphataemia, headache, flushing, dizziness and hypertension. Injection/infusion site reactions comprise several ADRs which individually are either uncommon or rare.

The most serious ADR is anaphylactoid/anaphylactic reactions (rare); fatalities have been reported.

Adverse drug reactions observed during clinical trials and post-marketing experience

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known[(1)]
Immune system disorders		Hypersensitivity	Anaphylactoid/anaphylactic reactions	
Metabolism and nutritional disorders	Hypophosphataemia			
Nervous system disorders	Headache, dizziness	Paraesthesia, dysgeusia		Loss of consciousness[(1)]
Psychiatric disorders			Anxiety[(2)]	
Cardiac disorders		Tachycardia		Kounis syndrome[(1)]
Vascular disorders	Flushing, hypertension	Hypotension	Phlebitis, syncope[(2)], presyncope[(2)]	

Respiratory, thoracic and mediastinal disorders		Dyspnoea	Bronchospasm[2]	
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia, abdominal pain, constipation, diarrhoea	Flatulence	
Skin and subcutaneous tissue disorders		Pruritus, urticaria, erythema, rash[3]	Angioedema[2], pallor[2], distant skin discolouration[2]	Face oedema[1]
Musculoskeletal and connective tissue disorders		Myalgia, back pain, arthralgia, pain in extremity, muscle spasms		Hypophosphataemic osteomalacia[1]
General disorders and administration site conditions	Injection/infusion site reactions[4]	Pyrexia, fatigue, chest pain, oedema peripheral, chills	Malaise, influenza like illness (whose onset may vary from a few hours to several days) [2]	
Investigations		Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased, blood alkaline phosphatase increased		

1 ADRs exclusively reported in the post-marketing setting; estimated as rare.

2 ADRs reported in the post-marketing setting which are also observed in the clinical setting.

3 Includes the following preferred terms: rash (individual ADR determined to be uncommon) and rash erythematous, -generalised, -macular, -maculo-papular, -pruritic (all individual ADRs determined to be rare).

4 Includes, but is not limited to, the following preferred terms: injection/infusion site -pain, -haematoma, -discolouration, -extravasation, -irritation, -reaction, (all individual ADRs determined to be uncommon) and -paraesthesia (individual ADR determined to be rare).

Note: ADR = Adverse drug reaction.

4.9 Overdose

Administration of FCM in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation. If iron accumulation has occurred, treat according to standard medical practice, e.g. consider the use of an iron chelator.

5. Pharmacological properties

1. Pharmacodynamic properties

Pharmacotherapeutic group: Iron trivalent, parenteral preparation, ATC code: B03AC FCM solution for injection/infusion is a colloidal solution of the iron complex ferric carboxymaltose. The complex is designed to provide, in a controlled way, utilisable iron for the iron transport and storage proteins in the body (transferrin and ferritin, respectively). Red cell utilisation of ^{59}Fe from radio-labelled FCM ranged from 91% to 99% in subjects with iron deficiency (ID) and 61% to 84% in subjects with renal anaemia at 24 days post-dose.

FCM treatment results in an increase in reticulocyte count, serum ferritin levels and TSAT levels to within normal ranges.

Clinical efficacy and safety

The efficacy and safety of FCM has been studied in different therapeutic areas necessitating intravenous iron to correct iron deficiency. The main studies are described in more detail below.

Cardiology

Chronic heart failure

Study CONFIRM-HF was a double-blind, randomised, 2-arm study comparing FCM (n=150) vs. placebo (n=151) in subjects with chronic heart failure and ID for a treatment period of 52 weeks. At Day 1 and Week 6 (correction phase), subjects received either FCM according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2), placebo or no dose. At Weeks 12, 24, and 36 (maintenance phase) subjects received FCM (500 mg iron) or placebo if serum ferritin was <100 ng/mL or 100–300 ng/mL with TSAT <20%. The treatment benefit of FCM vs. placebo was demonstrated with the primary efficacy endpoint, the change in the 6-minute walk test (6MWT) from baseline to Week 24 (33 ±11 metres, p=0.002). This effect was sustained throughout the study to Week 52 (36 ±11 metres, p<0.001).

Study EFFECT-HF was an open-label (with blinded endpoint evaluation), randomised, 2-arm study comparing FCM (n=86) vs. standard of care (n=86) in subjects with chronic heart failure and ID for a treatment period of 24 weeks. At Day 1 and Week 6 (correction phase), subjects received either FCM according to a simplified dosing grid using baseline Hb and body weight at screening (see section 4.2) or standard of care. At Week 12, (maintenance phase) subjects received FCM (500 mg iron) or standard of care if serum ferritin <100 ng/ml or 100 to 300 ng/ml and TSAT <20%. The treatment benefit of FCM vs. standard of care was demonstrated with the primary efficacy endpoint, the change in weight-adjusted peak VO_2 from baseline to Week 24 (LS Mean 1.04 ±0.44, p=0.02).

<u>Nephrology</u>

Haemodialysis-dependent chronic kidney disease

Study VIT-IV-CL-015 was an open-label, randomised parallel group study comparing FCM (n=97) to iron sucrose (n=86) in subjects with ID anaemia undergoing haemodialysis. Subjects received FCM or iron sucrose 2–3 times per week in single doses of 200 mg iron directly into the dialyser until the individually calculated cumulative iron dose was reached (mean cumulative dose of iron as FCM: 1,700 mg). The primary efficacy endpoint was the percentage of subjects reaching an increase in Hb of ≥1.0 g/dL at 4 weeks after baseline. At 4 weeks after baseline, 44.1% responded to treatment with FCM (i.e. Hb increase of ≥1.0 g/dL) compared to 35.3% for iron sucrose (p=0.2254).

Non-dialysis-dependent chronic kidney disease

Study 1VIT04004 was an open-label, randomised active-control study, evaluating the safety and efficacy of FCM (n=147) vs. oral iron (n=103). Subjects in the FCM group received 1,000 mg of iron at baseline and 500 mg of iron at days 14 and 28, if TSAT was <30% and serum ferritin was <500 ng/mL at the respective visit. Subjects in the oral iron arm received 65 mg iron TID as ferrous sulphate from baseline to day 56. Subjects were followed-up until day 56. The primary efficacy endpoint was the percentage of subjects achieving an increase in Hb of ≥1.0 g/dL anytime between baseline and end of study or time of intervention. This was achieved by 60.54% of subjects receiving FCM vs. 34.7% of subjects in the oral iron group (p<0.001). Mean haemoglobin change to day 56/end of study was 1.0 g/dL in the FCM group and 0.7 g/dL in the oral iron group (p=0.034, 95% CI: 0.0, 0.7).

Gastroenterology

Inflammatory bowel disease

Study VIT-IV-CL-008 was a randomised, open-label study which compared the efficacy of FCM vs. oral ferrous sulphate in reducing ID anaemia in subjects with inflammatory bowel disease (IBD). Subjects received either FCM (n=111) in single doses of up to 1,000 mg iron once per week until the individually calculated iron dose (per Ganzoni formula) was reached (mean cumulative iron dose: 1,490 mg), or 100 mg iron BID as ferrous sulphate (n=49) for 12 weeks. Subjects receiving FCM showed a mean increase in Hb from baseline to Week 12 of 3.83 g/dL, which was non-inferior to 12 weeks of twice daily therapy with ferrous sulphate (3.75 g/dL, p=0.8016).

Study FER-IBD-07-COR was a randomised, open-label study comparing the efficacy of FCM vs. iron sucrose in subjects with remitting or mild IBD. Subjects receiving FCM were dosed according to a simplified dosing grid using baseline Hb and body weight (see section 4.2) in single doses up to 1,000 mg iron, whereas subjects receiving iron sucrose were dosed according to individually calculated iron doses using the Ganzoni formula in doses of 200 mg iron until the cumulative iron dose was reached. Subjects were followed-up for 12 weeks. 65.8% of subjects receiving FCM (n=240; mean cumulative iron dose: 1,414 mg) vs. 53.6% receiving iron sucrose (n=235; mean cumulative dose 1,207 mg; p=0.004) had responded at Week 12 (defined as Hb increase ≥2 g/dL). 83.8% of FCM-treated subjects vs. 75.9%

of iron sucrose-treated subjects achieved a Hb increase ≥2 g/dL or had Hb within normal limits at Week 12 (p=0.019).

Women's health

Post partum

Study VIT-IV-CL-009 was a randomised open-label non-inferiority study comparing the efficacy of FCM (n=227) vs. ferrous sulphate (n=117) in women suffering from post-partum anaemia. Subjects received either FCM in single doses of up to 1,000 mg iron until their individually calculated cumulative iron dose (per Ganzoni formula) was reached, or 100 mg of iron as oral ferrous sulphate BID for 12 weeks. Subjects were followed-up for 12 weeks. The mean change in Hb from baseline to Week 12 was 3.37 g/dL in the FCM group (n=179; mean cumulative iron dose: 1,347 mg) vs. 3.29 g/dL in the ferrous sulphate group (n=89), showing non-inferiority between the treatments.

Pregnancy

Intravenous iron medicines should not be used during pregnancy unless clearly necessary. Treatment with FCM should be confined to the second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus.

Limited safety data in pregnant women are available from study FER-ASAP-2009-01, a randomised, open-label, study comparing FCM (n=121) vs. oral ferrous sulphate (n=115) in pregnant women in the second and third trimester with ID anaemia for a treatment period of 12 weeks. Subjects received FCM in cumulative doses of 1,000 mg or 1,500 mg of iron (mean cumulative dose: 1,029 mg iron) based on Hb and body weight at screening, or 100 mg of oral iron BID for 12 weeks. The incidence of treatment related adverse events was similar between FCM treated women and those treated with oral iron (11.4% FCM group; 15.3% oral iron group). The most commonly reported treatment-related adverse events were nausea, upper abdominal pain and headache. Newborn Apgar scores as well as newborn iron parameters were similar between treatment groups.

Ferritin monitoring after replacement therapy

There is limited data from study VIT-IV-CL-008 which demonstrates that ferritin levels decrease rapidly 2–4 weeks following replacement and more slowly thereafter. The mean ferritin levels did not drop to levels where retreatment might be considered during the 12 weeks of study follow up. Thus, the available data does not clearly indicate an optimal time for ferritin retesting although assessing ferritin levels earlier than 4 weeks after replacement therapy appears premature. Thus, it is recommended that further re-assessment of ferritin should be made by the clinician based on the individual patient's condition.

2. Pharmacokinetic properties

Distribution

Positron emission tomography demonstrated that ^{59}Fe and ^{52}Fe from FCM was rapidly eliminated from the blood, transferred to the bone marrow, and deposited in the liver and spleen.

After administration of a single dose of FCM of 100 to 1,000 mg of iron in ID subjects, maximum total serum iron levels of 37 µg/mL up to 333 µg/mL are obtained after 15 minutes to 1.21 hours respectively. The volume of the central compartment corresponds well to the volume of the plasma (approximately 3 litres).

<u>Elimination</u>

The iron injected or infused was rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours, the mean residence time (MRT) from 11 to 18 hours. Renal elimination of iron was negligible.

3. Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. Preclinical studies indicate that iron released from FCM does cross the placental barrier and is excreted in milk in limited, controlled amounts. In reproductive toxicology studies using iron replete rabbits FCM was associated with minor skeletal abnormalities in the fetus. In a fertility study in rats, there were no effects on fertility for either male or female animals. No long-term studies in animals have been performed to evaluate the carcinogenic potential of FCM. No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of FCM with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.

6. Pharmaceutical particulars

1. List of excipients

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

The compatibility with containers other than polyethylene and glass is not known.

4. Shelf life

Shelf life of the product as packaged for sale:

3 years.

Shelf life after first opening of the container:

From a microbiological point of view, preparations for parenteral administration should be used immediately.

Shelf life after dilution with sterile 0.9% m/V sodium chloride solution:

From a microbiological point of view, preparations for parenteral administration should be used immediately after dilution with sterile 0.9% m/V sodium chloride solution.

5. Special precautions for storage

Store in the original package in order to protect from light. Do not store above 30 °C. Do not freeze.

6. Nature and contents of container

FCM is supplied in a vial (type I glass) with a stopper (bromobutyl rubber) and an aluminium cap as:

– 2 mL solution containing 100 mg iron. Available in pack sizes of 1, 2 and 5 vials.

– 10 mL solution containing 500 mg iron. Available in pack sizes of 1, 2 and 5 vials.

– 20 mL solution containing 1,000 mg iron. Available in a pack size of 1 vial.

7. Special precautions for disposal and other handling

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FCM is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FCM must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction.(63)

In a multicenter, randomized, controlled study in 2008 by Melvin H. Seid et al performed on 291 women less than 10 days after delivery with hemoglobin 10 g/dL or less were randomized to receive ferric carboxymaltose (n=143) 1000mg or less intravenously over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) or ferrous sulphate (n=148) 325 mg orally thrice daily for 6 weeks. This study showed ferric carboxy maltose – treated subjects were significantly more likely to; (1) achieve a haemoglobin greater than 12 g/dL in a shorter time period with a sustained hemoglobin greater than 12 g/dL at day 42, (2) achieve hemoglobin rise 3 g/dL or greater more quickly, (3) attained higher serum transferrin saturation and ferritin levels drug related adverse events occurred less frequently with ferric carboxy maltose. Hence it was proved by the study that ferric carboxy maltose was safe and well tolerated with an efficacy superior to oral ferrous sulfate in the treatment of postpartum iron deficiency anemia.[7]

In an open, single arm study was conducted in 2017 by Vineet Mishra et al which included 615 women with diagnosis of iron deficiency anemia and haemoglobin (Hb) levels between 4 gm% and 11 gm% from January 2013 to december 2016. Intravenous Ferric Carboxy maltose (500 – 1500mg) was administered and the improvement in haemoglobin levels and iron stores were assessed after three weeks of total dose infusion. The results showed out of which 615 women, 595 women were included in the analysis. Most of the women were in the age group of 27-30 years. Most of the women had mild anemia as per world health organization guidelines. Mean haemoglobin levels significantly increased over a period of three weeks after ferrous carboxy maltose administration. Other parameters like total iron binding capacity, ferritin and iron also had a significant improvement after ferric carboxy maltose administration. No serious adverse events were observed after ferric carboxy maltose. Therefore it was concluded that intravenous ferric carboxy maltose was an effective and a safe treatment option for iron deficiency anemia and has an advantage of single administration of high dose without serious adverse effects.[5]

In a prospective observational study conducted by Bernd Froessler et al in 2014 on 65 anemic pregnant women received ferric carboxy maltose upto 15 mg/kg between 24 and 40 weeks of pregnancy (median 35 weeks gestational age, SD 3.6). Treatment effectiveness was assessed by repeat hemoglobin (Hb), peripheral smear, serum ferritin measurements and patient report of well-being in the postpartum period. Safety was assessed by analysis of adverse drug reactions and fetal heart rate monitoring during the infusion. Later results were interpreted which showed intravenous ferric carboxy maltose infusion significantly increased Hb values ($p<0.01$) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and upto 8 weeks post-partum which remained above baseline levels. Fetal heart rate monitoring did not indicate a drug related negative impact on the fetus. Of the 29 (44.6%) women interviewed, 19 (65.5%) women reported an improvement in their well-being and 9 (31%) felt no difference after the infusion. None of the women felt worse. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients. Hence by this prospective study it was concluded that the safe and effective use of ferric carboxy maltose in the treatment of iron deficiency anemia in pregnancy is consistent with the existing observational reports.

4.1 MATERIALS AND METHODS

"The present study was conducted in the department of obstetrics and gynaecology, KAHER Dr. Prabhakar Kore Hospital and medical Research Centre, Belagavi, Karnataka".

Study design :

Observational study

Study settings :

KAHER, Dr. Prabhakar Kore charitable Hospital, Belagavi.

Duration of data collection :

1 year 6 months

Study period :

January 2020 **–** June 2020

Study population :

Postpartum women admitted at KAHER, Dr. Prabhakar Kore charitable Hospital, Belagavi.

f)Sample size and statistical analysis :

Pre test Hb mean = 8.97

Post test Hb mean = 10.34

Pre test Hb SD = 2.99

Post test Hb SD = 4.97

Power of test = 90% (5% beta error)

Confidence = 99% (1% alpha error)

n = $(Sd/d)^2$ (Z alpha + Z beta) + 20% extra

= **90 pairs**

Z alpha = 2.58, Z beta = 1.682

Statistics (1) Dependent t / Wilcoxon matched pairs test

Selection criteria :

Inclusion criteria

Postpartum women more than 18 years of age with a diagnosis of anemia ranging between 7 gm% to 11 gm% of hemoglobin levels with iron deficiency anemia according to WHO classification of anemia.

Exclusion criteria

-History of anemia other than iron deficiency anemia

- Patients who received blood transfusion postpartum.

- Current treatment with myelosuppressive therapy

- Hemodynamic instability

- Women who developed allergic reactions to iron therapy previously

Ethical clearance :

Ethical clearance was obtained from ethical clearance committee, KAHER, J.N.Medical college Belagavi on 24-12-2019.

Consent form :

Postpartum women who are fulfilling selection criteria at department of obstetrics and gynaecology at KAHER Dr. Prabhakar Kore hospital and Medical Research Centre were obtained after briefing about the nature of the study, detailed written consent was obtained.

Data collection :

Demographic data like age, education qualification, socioeconomic status was obtained. The weight and height of the participants were recorded using standard methodology recorded on a predesigned and pretested proforma.

All postpartum women will be selected on the bases of inclusion criteria and to be given informed written consent before participation in the study.

Protocol followed in the study :

Postpartum women with the history of anemia other than iron deficiency anemia, on treatment with myelosuppressive therapy, women with hemodynamic instability and who had developed allergic reactions to iron therapy previously were excluded from the study as per the exclusion criteria. Patients hemoglobin levels , peripheral smear and serum ferritin levels were obtained.

The total required dose of Ferric Carboxy Maltose (FCM) was calculated using

Ganzoni formula :

Iron requirement = Body weight (kg) x 2.3 x (150 – Patient's hemoglobin gm/dl) + 500 or 1000mg (for stores).

The recommended dose of FCM was not exceed 1500mg of iron (30ml) per day. FCM was administered as an infusion diluted in sterile 0.9% sodium chloride (Nacl) solution. FCM injection, 500mg was diluted with 100ml Nacl and administered over 6 minutes. Doses between 1000mg to 1500mg required dilution with 250ml Nacl and administration time of 15 minutes. The drug was administered under supervision and infusion was stopped in case of any side effects.

Side effects :

- Local reactions
- Diarrhea
- Nausea
- Pain abdomen
- Vomiting
- Urticaria

- Headache
- Hypotension
- Myalgia
- Severe anaphylactic reactions

If any hypersensitivity reactions or signs of intolerance occured during administration, the treatment was stopped immediately. Treatment with antihistamines (inj. Avil 2ml stat and inj. hydrocortisones 5ml stat and/or 1:1000 adrenaline was given.

The women were followed up after three to four weeks of total dose of FCM infusion to assess the hemoglobin status.

Outcome :

The primary outcome was assessed after three to four weeks of total dose of FCM infusion for the rise in hemoglobin and serum ferritin levels. The secondary severity of Side effects as mentioned above developed in the women with FCM infusion. Outcome was assessed on the basis of number and severity of side effects

RESULTS

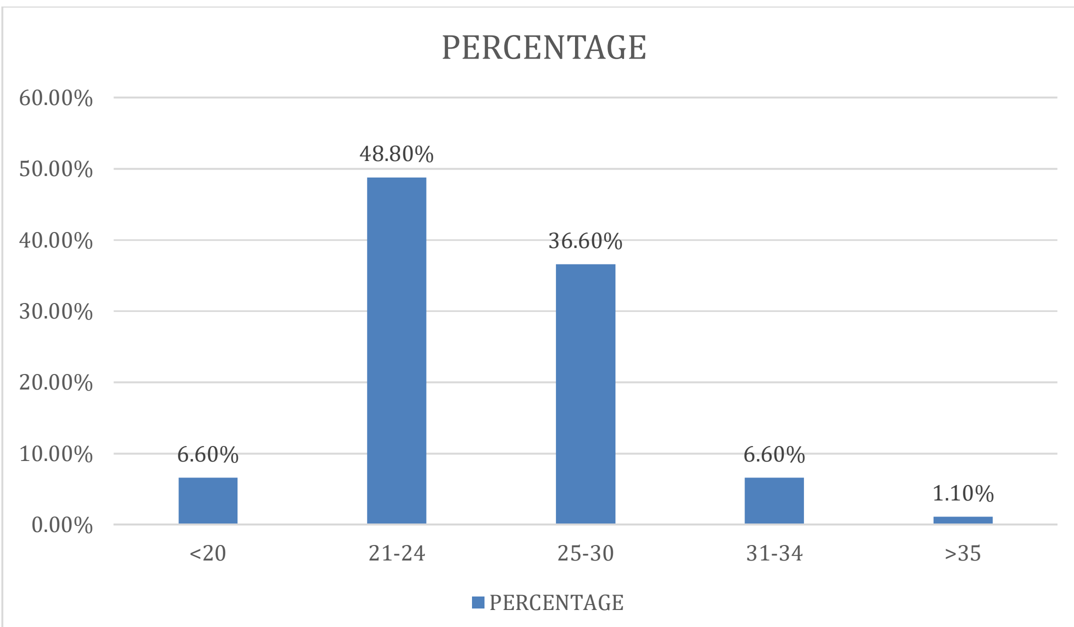
The present study was conducted in the department of obstetrics and Gynaecology, KAHER Dr. Prabhakar Kore hospital and medical research institute, Belagavi from January 2020 to June 2021

The minimal sample size was 90 postpartum women with diagnosis of iron deficiency anemia.

DISTRIBUTION BY AGE:

Table 1. Distribution according to age.

AGE	NUMBER	PERCENTAGE
<20	6	6.6 %
21-24	44	48.8%
25-30	33	36.6%
31-34	6	6.6%
>35	1	1.1%
TOTAL	90	100%



Graph 1. Distribution according to age.

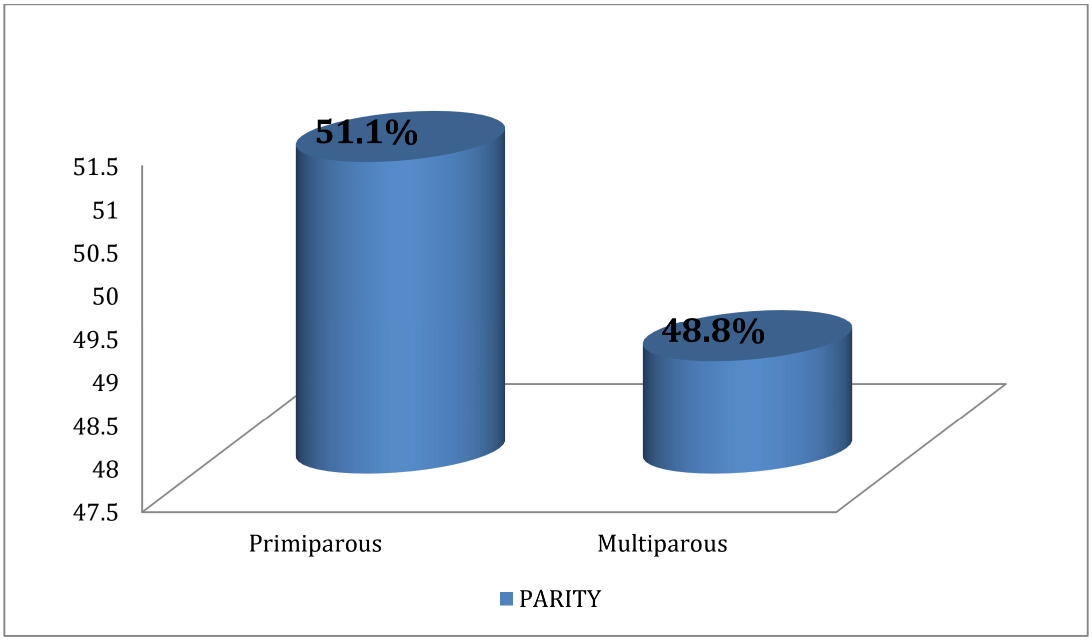
In this study, the common age group among the study patients was between 20 to 24 years(48.8%) and only one patient was more than 35 years of age.

DISTRIBUTION BY PARITY :

Table 2: Distribution by parity

PARITY	NUMBER	PERCENTAGE
PRIMI	46	51.1%
MULTI	44	48.8%
TOTAL	90	100%

About 51.1 % percent of our study population were primiparaous and about 48.8% were multiparous women.



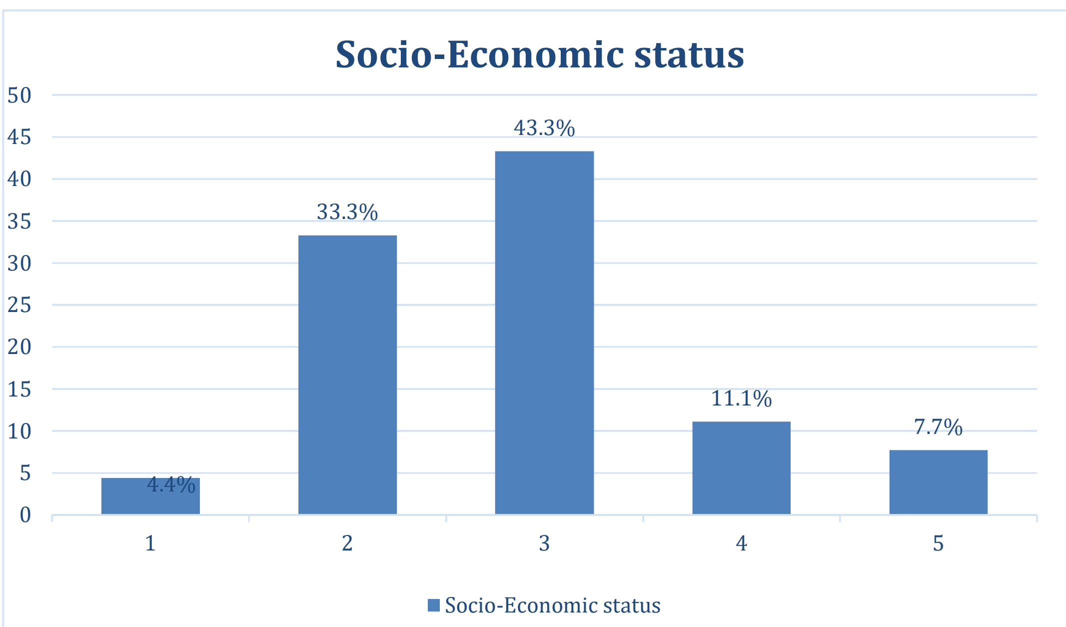
Graph 2. Distribution according to parity.

SOCIOECONOMIC STATUS:

Table 3. Distribution according to socioeconomic status.

SOCIOECONOMIC STATUS	NUMBER	PERCENTAGE %
1	4	4.4
2	30	33.3
3	39	43.3
4	10	11.1
5	7	7.7
TOTAL	90	100.00

Higher number of women (43.3%) were falling under class lll socio economic class according to modified B.J. Prasad classification.



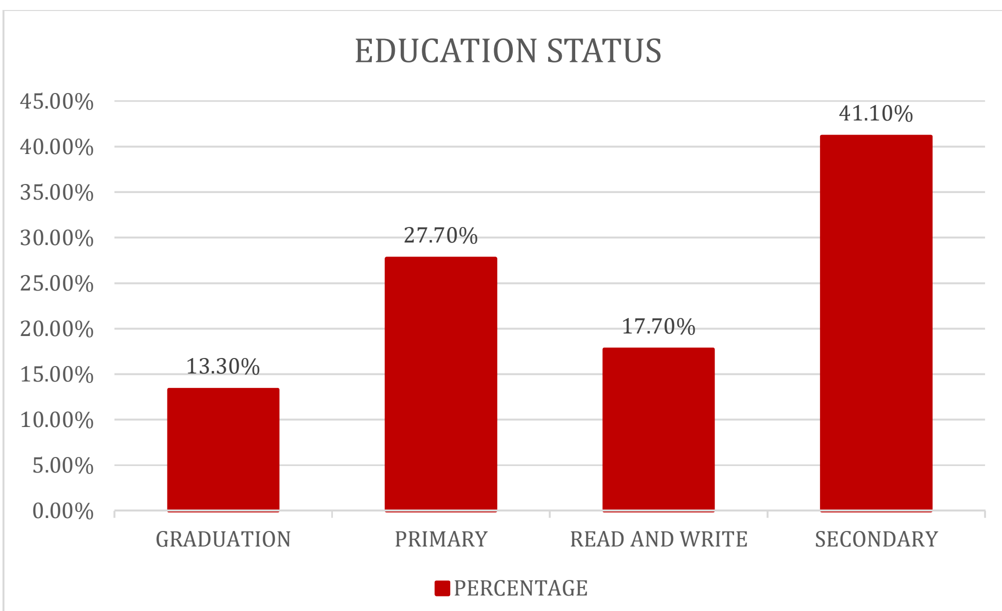
Graph 3. Distribution according to Socio-economic status.

DISTRIBUTION BY EDUCATION. :

Table 4. Distribution according to education.

EDUCATION	NUMBER	PERCENTAGE
GRADUATION	12	13.3%
PRIMARY	25	27.7%
READ AND WRITE	16	17.7%
SECONDARY	37	41.1%
TOTAL	90	100%

With regard to educational status most of the women had completed their secondary education(41.1%) and no patients were illiterates.



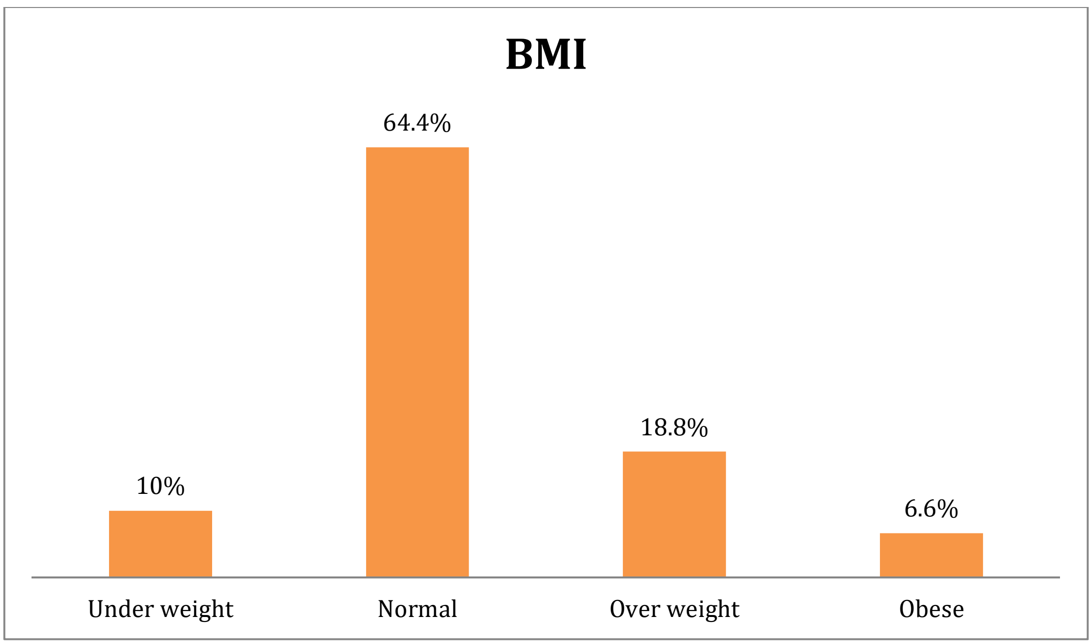
Graph 4. Distribution according to education status.

DISTRIBUTION ACCORDING TO BMI :

Table 5. Distribution according to BMI.

BMI	NUMBER	PERCENTAGE
UNDER WEIGHT	9	10%
NORMAL	58	64.4%
OVER WEIGHT	17	18.8%
OBESE	6	6.6%
TOTAL	90	100%

On examination of height and weight BMI was calculated, majority of the study patients were normal weight (64.4%) and about 10% women were underweight.

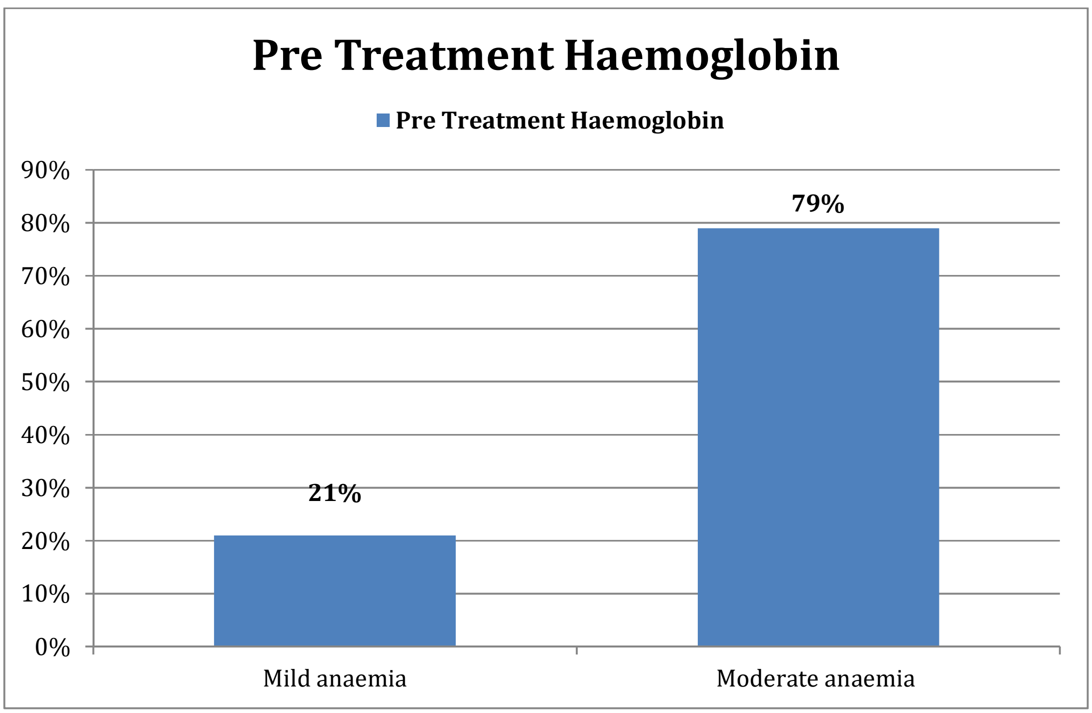


Graph 5. Distribution according to BMI.

PRE TREATMENT HEMOGLOBIN

Table 6. Distribution according to pre treatment hemoglobin levels.

	NUMBER OF PATIENTS	PERCENTAGE
MILD ANEMIA (10 to 10.9 gm/dl)	19	21%
MODERATE ANEMIA (7 to 9.9 gm/dl)	71	79%



Graph 6. Distribution according to Pre treatment hemoglobin levels in percentage.

Table 7. Mean hemoglobin before treatment.

HEMOGLOBIN BEFORE TREATMENT			
MEAN	**S.D.**	**MIN**	**MAX**
9.36	0.84	7.1	10.8

Post delivery hemoglobin was sent after 12-24 hours of delivery. About 19 patients had mild anemia, 71 patients were having moderate anemia. The mean hemoglobin pre treatment was 9.3 gm/dl.

BASELINE CHARACTERISTICS OF STUDY POPULATION:

	MEAN	**S.D.**	**MIN**	**MAX**
HEIGHT	158.10	7.05	138	172
WEIGHT	54.23	7.37	40	75
BMI	21.66	2.44	15.8	29.2
BLOOD LOSS AT DELIVERY	339.33	131.00	80	680
PCV	28.82	2.82	19.7	34.5
FERRITIN	50.3	42.14	50.3	143.7

Table 8. Distribution of study population according to baseline characteristics.

The mean blood loss at delivery was 339.3ml, mean packed cell volume was 28.8%. The peripheral smear of all study subjects was confirmed to be microcytic hypochromic anemia.

IRON DEFICIT:

Table 9. Iron deficit

	MEAN	S.D.	MIN	MAX
IRON DEFICIT	832.97	123.97	595	1170.3

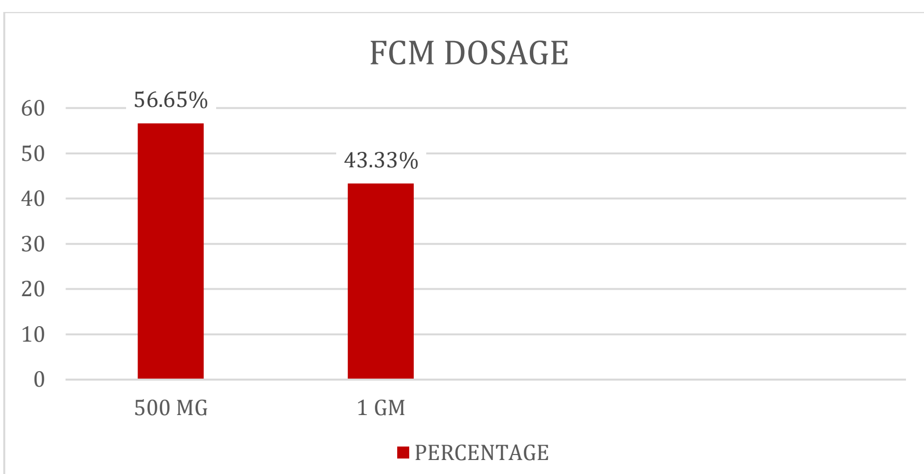
The iron deficit in the study population was calculated by using Ganzoni's formula. The mean iron deficit among the patients was 832.9gms. The minimum iron deficit was 595gms and maximum was 1170.3gms.

DISTRIBUTION BY DOSE OF FCM:

Table 10. Distribution of study population according to dosage of FCM given.

FCM GIVEN	NUMBER	PERCENTAGE
500 MG	51	56.65%
1 GM	39	43.33%
TOTAL	90	100.00

Most of them received 500mg FCM infusion (56.6%) and about 43.3% of the women received 1 gm FCM.



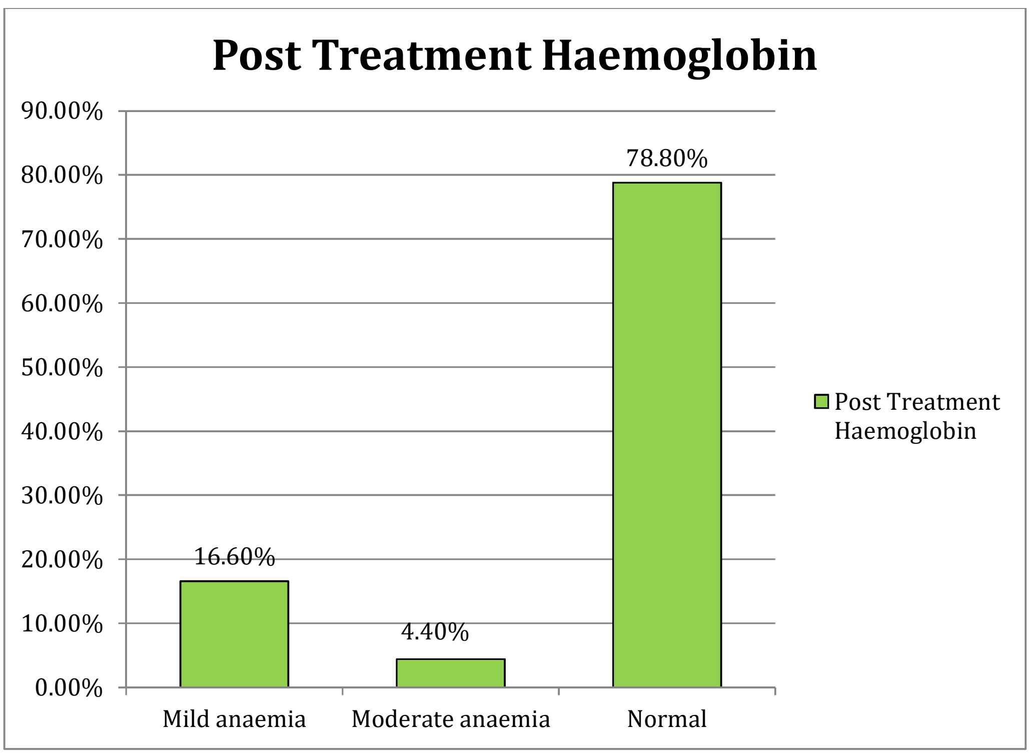
Graph 7. Distribution according to dosage of FCM given.

POST TREATMENT HEMOGLOBIN

Table 11. Post treatment hemoglobin**.**

	NUMBER OF PATIENTS	PERCENTAGE
MILD ANEMIA (10 to 10.9 gm/dl)	15	16.6%
MODERATE ANEMIA (7 to 9.9 gm/dl)	4	4.4%
NORMAL (>11 gm/dl)	71	78.8%

In this study post treatment hemoglobin was done and most of them were normal hemoglobin i.e. about 71 women, 15 were mild and 4 were moderate anemia after treatment with injection FCM.



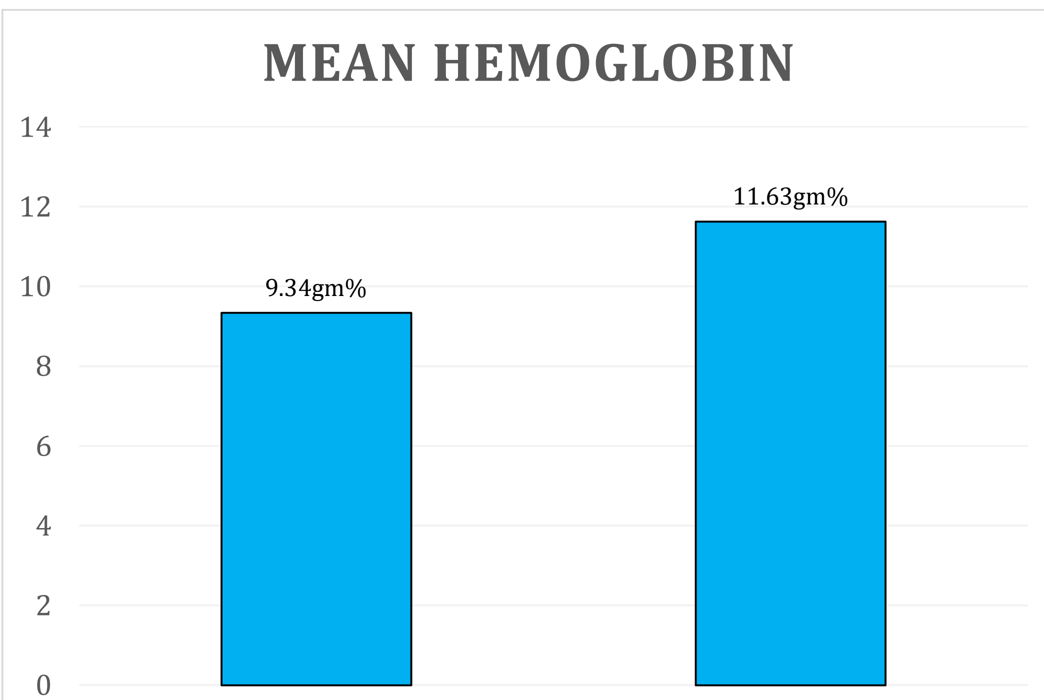
Graph 8. Distribution according to Post treatment hemoglobin levels in percentage.

Table 12. Statistical significance of pre and post treatment Hemoglobin.

HEMOGLOBIN BEFORE TREATMENT			
MEAN	**S.D.**	**MIN**	**MAX**
9.36	0.84	7.1	10.8

HEMOGLOBIN ON F0LLOW UP			
MEAN	**S.D.**	**MIN**	**MAX**
11.63	0.83	9.2	13.4

The mean hemoglobin level before treatment with FCM was 9.36 gm/dl after three to four weeks of treatment with FCM, the mean hemoglobin was raised to 11.63 gm/dl. **The p value was calculated using student's paired t test which was less than 0.0001.**



Graph 9. Comparison between hemoglobin before and after treatment.

Table 13. Mean rise in hemoglobin after injection FCM.

	MEAN	S.D.	MIN	MAX
PERCENTAGE RAISE IN HEMOGLOBIN	**2.29**	0.41	1.4	3.2

The minimum raise in hemoglobin was 1.4 gm%, maximum raise was 3.2 gm% and mean rise in hemoglobin after treatment with injection FCM is found to about 2.29 gm%.

SIDE EFFECTS :

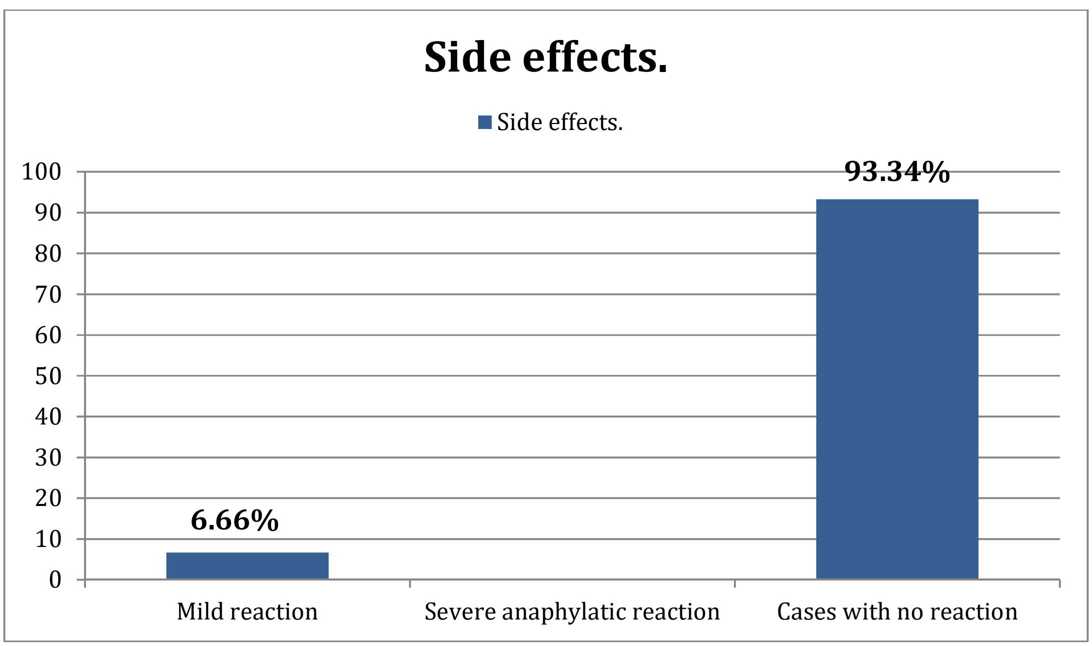
Table 14. Patients having side effects.

SIDE EFFECTS	NUMBER OF PATIENTS
NAUSEA	3
VOMITING	1
HEADACHE	1
MAYALGIA	1
PAIN ABDOMEN	0
URTICARIA	0
LOCAL REACTIONS	0
HYPOTENSION	0
DIARRHOEA	0
SEVERE ANAPHYLACTIC REACTIONS	0
TOTAL	**6**

Table 15. Distribution according to severity of side effects

REACTION TO FCM	NUMBER OF CASES	PERCENTAGE
MILD REACTION	6	6.66%
SEVERE ANAPHYLACTIC REACTION	0	0
CASES WITH NO REACTIONS	84	93.34%
TOTAL	**90**	**100%**

Side effects during and after FCM infusion was noted. There were 6 patients who had minor adverse reactions like nausea (3), vomiting (1), headache (1) and myalgia (1). No patient had severe anaphylactic reaction.



Graph 10. Distribution according to severity of side effects.

DISCUSSION

Iron deficiency anemia is the most common cause of anemia in postpartum period about 37% reported in 1st postpartum week. Postpartum anemia is precipitated because of inadequate iron intake prior to and during pregnancy and by peripartum blood loss. About 10% women in postpartum have hemoglobin less than 8gm/dl. Overall prevalence of anemia in lactating women is 58% in India.

Treatment of postpartum anemia is absolutely necessary as it may lead to complications as puerperal sepsis, subinvolution of uterus and lactational failure. Postpartum anemia is also associated with cognitive impairment, depression, stress and anxiety. It also, adds to increased hospital stay, high hospital expenses and more likely to receive a blood transfusion.

The currently available methods for treatment in postpartum anemia are oral iron preparations, i.v. iron and blood transfusion.

Oral iron therapy is the first line of treatment for postpartum anemia especially when hemoglobin is between 9 to 11 gm/dL. Inflammatory reaction secondary to surgically assisted deliveries leads to sequestration of iron in macrophages and decreases intestinal absorption so that administered iron is not available for erythropoiesis.

Blood transfusion is reserved option for severe anemia when hemoglobin is less than 7 gm/dl and during emergency like postpartum hemorrhage as a life saving measure. It has got risk of transfusion related reactions, immunological interactions and infections.

There are multiple i.v. iron formulations available like iron sucrose, iron dextran which are second generation i.v. preparations. These second generation i.v. iron compounds come with drawbacks such as they typically require multiple transfusions hence multiple hospital visits, they are less robust iron-carbohydrate formulations. There is chances of accumulation in the blood might result in potential reactions.

Ferric Carboxy maltose is a newer parenteral iron preparation, which is dextran free, hence overcomes the limitations of existing i.v. preparations. FCM complex is composed of polynuclear iron hydroxide complexed to carboxy maltose. It is a strong and robust iron complex. It can be administered in high doses, does not release large amount of free iron (reactive) into circulation and does not trigger immunogenic reactions. FCM can be administered in a single dose up to 1000ml in 15 to 20 min. It has the ability to increase Hb 2gm/dl or greater. FCM is cost effective, can be administered in single dose in one hospital visit. It has lesser side effects, reduced interruption in lifestyle and improved patient compliance.

This observational study was conducted in the department of obstetrics and gynaecology, KAHER Dr. Prabhakar Kore hospital and medical research centre, Belagavi.

A total of 90 postnatal women with iron deficiency anemia who received injection ferric carboxy maltose were included under the study. The study was conducted from January 2020 to June 2021. Iron deficiency anemia was confirmed by post delivery hemoglobin levels (12-24 hours post delivery), packed cell volume, peripheral smear and serum ferritin levels. In the meantime, adverse reaction during and post FCM injection was noted. Then the patient was followed up for repeat hemoglobin after 3 to 4 weeks post FCM infusion and looked for percentage raise in hemoglobin. Due to COVID pandemic a few study patients were followed up hemoglobin report was documented over telephonic conversation.

In this study, the common age group among the study patients was between 20 to 24 years (48.8%) and only one patient was more than 35 years of age. Higher number of women (43.3%) were falling under class lll socio economic class according to modified B.J. Prasad classification. With regard to educational status most of the women had completed their secondary education (41.1%) and no patients were illiterates.

In the present study, most of the women were primipara (51.1%) and most of them underwent cesarean section (61.1%) as mode of delivery. On examination of height and weight BMI was calculated, majority of the study patients were normal weight (64.4%) and about 10% women were underweight.

Post delivery hemoglobin was sent after 12-24 hours of delivery. About 19 patients had mild anemia, 71 patients were having moderate anemia. The mean hemoglobin pretreatment was 9.3 gm/dl. The mean iron deficit among the patients was 832.9gms. Most of them received 500mg FCM infusion(56.6%). Adverse reactions during and after FCM infusion was noted. There were 6 patients who had minor adverse reactions like nausea(3), vomiting(1), headache(1) and myalgia(1). No patient had severe anaphylactic reaction.

In this study post treatment hemoglobin was done and most of them were normal hemoglobin i.e. about 71 women, 15 were mild and 4 were moderate anemia after treatment with injection FCM. The mean post treatment hemoglobin was 11.6 gm/dl and the mean percentage raise in hemoglobin was 2.2 gm.

The p value was calculated using student's paired t test which was less than 0.0001 which suggests p value is highly significant. These study findings suggest that treatment of anemia with intravenous ferric carboxymaltose is effective and safe in treating iron deficiency anemia in postpartum women.

In a multicenter, randomized, controlled study in 2008 by Melvin H. Seid et al performed on 291 women less than 10 days after delivery with hemoglobin 10 g/dL or less were randomized to receive ferric carboxymaltose (n=143) 1000mg or less intravenously over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2500 mg) or ferrous sulphate (n=148) 325 mg orally thrice daily for 6 weeks. This study showed ferric carboxy maltose – treated subjects were significantly more likely to ; (1) achieve a haemoglobin greater than 12 g/dL in a shorter time period with a sustained hemoglobin greater than 12 g/dL at day 42, (2) achieve hemoglobin rise 3 g/dL or greater more quickly, (3) attained higher serum transferrin saturation and ferritin levels drug related adverse events occurred less frequently with ferric carboxy maltose. Hence it was proved by the study that ferric carboxy maltose was safe and well tolerated with an efficacy superior to oral ferrous sulfate in the treatment of postpartum iron deficiency anemia.

"In an open, single arm study was conducted in 2017 by Vineet Mishra et al which included 615 women with diagnosis of iron deficiency anemia and hemoglobin (Hb) levels between 4 gm% and 11 gm% from January 2013 to december 2016. Intravenous Ferric Carboxy maltose (500 – 1500mg) was administered and the improvement in hemoglobin levels and iron stores were assessed after three weeks of total dose infusion. The results showed out of which 615 women, 595 women were included in the analysis. Most of the women were in the age group of 27-30 years. Most of the women had mild anemia as per world health organization guidelines. Mean hemoglobin levels significantly increased over a period of three weeks after ferrous carboxy maltose administration. Other parameters like total iron binding capacity, ferritin and iron also had a significant improvement after ferric carboxy maltose administration. No serious adverse events were observed after ferric carboxy maltose. Therefore it was concluded that intravenous ferric carboxy maltose was an effective and a safe treatment option for iron deficiency anemia and has an advantage of single administration of high dose without serious adverse effects”.[1]

“In a prospective observational study conducted by Bernd Froessler et al in 2014 on 65 anemic pregnant women received ferric carboxy maltose upto 15 mg/kg between 24 and 40 weeks of pregnancy (median 35 weeks gestational age, SD 3.6). Treatment effectiveness was assessed by repeat hemoglobin (Hb), peripheral smear, serum ferritin measurements and patient report of well-being in the postpartum period. Safety was assessed by analysis of adverse drug reactions and fetal heart rate monitoring during the infusion. Later results were interpreted which showed intravenous ferric carboxy maltose infusion significantly increased Hb values ($p<0.01$) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and upto 8 weeks post-partum which remained above baseline levels. Fetal heart rate monitoring did not indicate a drug related negative impact on the fetus. Of the 29 (44.6%) women interviewed, 19 (65.5%) women reported an improvement in their well-being and 9 (31%) felt no different after the infusion. None of the women felt worse. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients. Hence by this prospective study it was concluded that the safe and effective use of ferric carboxy maltose in the treatment of iron deficiency anemia in pregnancy is consistent with the existing observational reports.”

“A comparative, interventional, prospective study was carried out by Mayank lunagariya et al, in 100 postpartum patients with Anemia (Hb level between 7 to 11 gm/dl) in the department of obstetrics and gynaecology, Government Medical College, Bhavnagar, Gujarat, India from June 2016 to July 2017. The subjects were randomized in two groups. First group receiving 1000 mg of intravenous iron sucrose divided in five doses on alternate days (200 mg each) and Second group receiving 1000 mg of intravenous ferric carboxymaltose. Results: Maximum number of patients in our study were belonged to low socioeconomic group, significantly higher number of women achieved rise of Hb >2gm/dl in FCM group.26 women in FCM group achieve Hb rise of >2gm/dl as compared to only 11 in iron sucrose group, which was highly significant (pvalue<0.001). Mean rise of Hb was 1.9 gm/dl for FCM group and 1.66gm/dl for iron sucrose group, which was also significant. Serum ferritin level in ferric carboxymaltose group was rises more (83.9 ng/ml) as compared to (76.06 ng/ ml) iron sucrose group. Unpaired‘t’ test was used to test the significance of rise and compare the rise between two groups. They concluded that Ferric carboxymaltose is an efficient and better alternative to Iron Sucrose in treating postpartum anemia. It has an added advantage of single dose regime with lower side effects”.54

“A prospective, interventional follow-up study was by Shashi Kant et al, from August to December 2018. One hundred eligible postpartum women with Hb level of 5–9.9 g/dl were administered a calculated dose of intravenous FCM based on Ganzoni’s formula with Hb target of 12 g/dl. Hb and serum ferritin were measured at baseline and at 6 weeks after FCM infusion and compared for mean increase. They found that there was a significant increase in Hb and serum ferritin levels after administration of FCM. The mean (95% confidence interval) increase in the Hb and serum ferritin after 6 weeks was 4.2 (3.9–4.5) g/dl and 137.3 (113.6–161.0) ng/ml, respectively. No major adverse events were reported. They found that administration of FCM was safe and effective in the treatment of moderate-to-severe anemia among postpartum women.55

In a study conducted by Setu Rathod et al, A total of 366 women admitted to SCB Medical College, Cuttack between September 2010 and August 2012 suffering from PPA hemoglobin (Hb) < 0.0001) than conventional iron sucrose and oral iron group. The mean increase in Hb after 2 weeks was 0.8, 2.4, and 3.2 g/dL and 2.1, 3.4, and 4.4 g/dL at 6 weeks in oral iron, iron sucrose and FCM groups, respectively. The mean increase in serum ferritin levels after 2 weeks was 2.5, 193.1, and 307.1 and 14.2, 64, and 106.7 ng/mL after 6 weeks in oral iron, iron sucrose and FCM groups, respectively. Adverse drug reactions were significantly less (P < 0.001) in FCM group when compared with other two groups. Conclusion: Ferric carboxymaltose elevates Hb level and restores iron stores faster than IV iron sucrose and oral iron, without any severe adverse reactions. There was better overall satisfaction reported by the patients who received FCM treatment."56

"In a study conducted by Urvashi Verma et al, 100 cases with iron deficiency anemia in post-partum patient were selected from postpartum wards and assigned in two groups of 50 each. In group A iron carboxymaltose injection administered by intravenous infusion up to a maximum single dose of 20 ml of iron carboxymaltose injection (1000 mg of iron). In group B Iron sucrose was given as 200mg elemental iron (2 ampules of 5 ml) in 100ml of 0.9% normal saline infusion over 15 min alternate days up to 5 days. All patients were monitored for rise in hemoglobin level and any adverse effect at 2 weeks, 4 weeks, 8 weeks and 12 weeks of iron therapy. They found that in group A mean Hemoglobin level rise is 3.95 g/dl and in group B it is 3.32 g/dl at 4 weeks of initial therapy. In group A 100% cases achieved target hemoglobin at 12 weeks after therapy while in group B 98% cases achieved target hemoglobin at 12 weeks after therapy. In group A 12% cases have grade 1 adverse reaction while in group B 20% cases have adverse reaction. They concluded that administration of intravenous iron has a good clinical result, with minimum adverse reactions. Thus we can conclude that intravenous ferric carboxymaltose therapy is safe, convenient, more effective and faster acting than intravenous iron sucrose for treatment of severe iron deficiency anemia in postpartum patient.

Strength of our study:

- Single dose of ferric carboxy maltose is effective in raising hemoglobin levels by 2.29 gm/dl in the span of three to 4 weeks duration with fewer side effects.
- All confounding factors were eliminated in the subjects who received injection FCM.

Limitations of our study:

- In the present study the sample size was less due to COVID pandemic during the study period.
- Many patients were not affordable for injection FCM

CONCLUSION

- The Present study showed that intravenous Ferric Carboxy Maltose offers rapid replacement of haemoglobin in body during post-partum period.
- Average increase in hemoglobin was 2.2 gm/dl with single dose of FCM.
- Clinical benefit with ferric carboxy maltose was achieved without significant adverse effects.

SUMMARY

Ferric Carboxy maltose has been recently introduced for the treatment of anemia. The present study was planned to study the efficacy and safety of Ferric Carboxy Maltose in the treatment of iron deficiency anemia among postpartum women.

The present study is one and half year observational study done from January 2020 to June 2021 in the department of obstetrics and gynaecology at KAHER Dr. Prabhakar Kore and Medical research centre, Belgaum. A total of 90 postpartum women were studied.. In this study, the common age group among the study patients was between 20 to 24 years (48.8%) and only one patient was more than 35 years of age. Higher numbers of women (43.3%) were falling under class lll socio economic class according to modified B.J. Prasad classification. With regard to educational status most of the women had completed their secondary education (41.1%) and no patients were illiterates. On examination of height and weight BMI was calculated, majority of the study patients were normal weight (64.4%) and about 10% women were underweight. Post delivery hemoglobin was sent after 12-24 hours of delivery. About 19 patients had mild anemia, 71 patients were having moderate anemia. The mean hemoglobin pretreatment was 9.3 gm/dl. Peripheral smear and serum ferritin levels were obtained. Iron deficiency anemia was confirmed by peripheral smear.

The total required dose of Ferric Carboxy Maltose (FCM) will be calculated using Ganzoni's formula. The mean iron deficit of the study population using was 832.9 gms.

The dose of injection FCM was given according to the iron deficit obtained. Most of them received 500mg FCM infusion (56.6%) and rest of them received 1 gm FCM.

Adverse reactions during and after FCM infusion was noted. There were 6 patients who had minor adverse reactions like nausea (3), vomiting(1), headache(1) and myalgia(1). No patient had severe anaphylactic reaction.

In this study post treatment hemoglobin was done after 3 to 4 weeks of inj. FCM and most of them were normal hemoglobin i.e. about 71 women, 15 were mild and 4 were moderate anemia after treatment with injection FCM.

The minimum raise in hemoglobin was 1.4 gm%, maximum raise was 3.2 gm% and mean rise in hemoglobin after treatment with injection FCM is found to about 2.29 gm%. The p value was calculated using student's paired t test which was less than 0.0001.

Intravenous Ferric Carboxy Maltose is more effective in the treatment of iron deficiency anemia among postpartum women. Further FCM is well tolerated with fewer side effects.

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ANNEXURE I: ETHICAL CLEARANCE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)

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E-Mail : dome@jnmc.edu

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Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 195 **Date: 24/12/2019**

To,
REG NO. BJ0119008
PG student in Obstetrics and Gynecology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"EFFICACY AND SAFETY OF INTRAVENOUS FERRIC CARBOXY MALTOSE IN IRON DEFICIENCY ANEMIA DURING POST-PARTUM PERIOD "**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

9

ANNEXURE II – INFORMED CONSENT FORM.

Title of Research Study: "Efficacy and safety of intravenous Ferric Carboxy Maltose in iron deficiency anaemia during post-partum period: one year hospital based observational study"

Principal investigator:

Dr. _________________

D and Professor,

Department of Obstetrics and Gynecology,

J. N. Medical college, Belagavi

Co- investigator

REG NO. BJ0119008HO

Post Graduate,

Department of Obst Gynecology,

J. N. Medical college, Belagav

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mrs. ____________________________ we are requesting you to enroll yourself in study titled "efficacy and safety of intravenous Ferric Carboxy Maltose in iron deficiency anaemia during post-partum period: one year hospital based observational study" conducted by **REG NO. BJ0119008HO**, Post Graduate in M.S. Obstetrics and Gynecology under the guidance of Dr. ___________, Department of Obstetrics and Gynecology, J.N. Medical College, KAHER Belagavi.

The purpose of research study is to know the efficacy of Ferrous Carboxymaltose and its potentiality to improve haemoglobin levels in postpartum iron deficiency anaemia and also study its safety. I will be the investigator for the study. This study is not being funded. I am going to give you information about this research project. Before you decide, you can talk to anyone you feel comfortable with about the research.

PURPOSE OF THE STUDY:

Iron deficiency anemia is the most common cause of anemia in the post partum period. Postpartum anemia is caused primarily by inadequate iron intake prior to and during pregnancy and by peripartum blood loss. Effects of iron deficiency during pregnancy and post-partum period include – fatigue, cardio-respiratory problems, increased chances of infection, reduced immunity, lactation failure, increased post-partum hemorrhage, longer hospital stay and hence increased hospital costs, are more likely to receive a blood transfusion.-

Intravenous iron dextran is known to cause life-threatening hypersensitivity reaction, anaphylactoid reactions, arthralgia, myalgia and/or fever, its use has been restricted by the necessity of a test dose, a black box warning in the package insert, and a maximum approved dose of 100 mg per day. Although the incidence of anaphylaxis and other adverse reactions with newer intravenous agents (eg, iron sucrose, ferric gluconate) is markedly lower, multiple doses and prolonged infusion times are typically required. Ferric Carboxy Maltose (FCM) has the ability to be injected safely in a single dose as large as 1000mg over 15 minutes. In a recently published non-inferiority trial of postpartum iron deficiency anemia found that intravenous ferric carboxy maltose was as effective as oral iron in increasing Hb 2 g/dL or greater.

FCM is cost effective with other positive benefits of fewer hospital visits and improved patient compliance. This study assessed the efficacy and safety of intravenous FCM in the post-partum women with iron deficiency anemia.

TYPE OF STUDY:

This study is intervensional study. It involves administration of injection Ferric Carboxy Maltose (FCM) by intravenous route during postpartum period and followup after 3-4 weeks after FCM injection to see in raise of hemoglobin levels and serum ferritin levels.

PARTICIPATION SELECTION :

We are inviting all postpartum women who are admitted in our hospital to participate in this study.

VOLUNTARY PARTICIPATION:

Your participation in research is voluntary. It is our choice whether to participate or not. Your decision whether to participate in the study or not will not change present or future health care services offered to you and will not affect your relationship with J. N. Medical College. If you choose not to participate in the study, you will still be offered the routine treatement in management of postpartum anemia that is given in our hospital. You will continue to receive the routine post natal care at our hospital even if you decline to participate in the study. If you decline to participate you are free to withdraw at any time.

INFORMATION ON THE DRUG :

The drug we are testing is Ferric Carboxy Maltose (FCM) which is being used in the treatment of iron deficiency anemia. The drug is used in the treatment of iron deficiency anemia in the postpartum period. You should know that that drug has a few side effects like nausea, vomiting, headache, dizziness, hypertension and rarely anaphylactoid reaction may occure. You will be monitored every 15 minutes for the first 1 hour of FCM injection to look for any of the side effects and appropriate treatement will be given for the same.

PROCEDURE INVOLVED :

If you agree to enroll yourself in my study, your detailed past history will be taken to know if you are eligible for the study. If you have any of the exclusion criteria you will not be enrolled in this study as your safety is the primary concern. If you are eligible to participate in this study, after taking consent your Patients hemoglobin levels , peripheral smear and serum ferritin levels will be obtained. Inj. FCM was administered as an infusion diluted in sterile 0.9% sodium chloride (Nacl) solution. FCM injection, 500mg can be diluted with 100ml Nacl and administered over 6 minutes. Doses between 1000mg to 1500mg require dilution with 250ml Nacl and administration time of 15 minutes. The drug is to be administered under supervision and infusion to be stopped in case of any side effects. You will be followed up after three weeks of total dose of FCM infusion to assess the hemoglobin and serum ferritin status.

SIDE EFFECTS :

As already mentioned there could be some side effects of this drug like nausea, vomiting, headache, dizziness, hypertension and rarely anaphylactoid reaction. If you develop any of adverse effects you will be treated for the same. In such a cases we will discuss together and you will be consulted regarding whether you wish to continue this study.

RISKS :

By participating in this research, there is a possibility that you will experience adverse effects of the drug. There is also a possibility that the drug may not work as well as are expecting it to. If any of these conditions arise, you will be given the routine treatement which is offered at our hospital nfor treating the postpartum iron deficiency anemia.

BENEFITS :

The benefits of taking part in this study is your participation being valuable contribution to medical research to improvise treatment currently practiced in the treatment of postpartum iron deficiency anemia.

FINANCIAL INCENTIVES FOR PARTICIPATION :

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research.

PRIVACY AND CONFIDENTIALITY :

The only people who will know that you are the research team. No information about you or information provided by you during the research will be disclosed to others without your written permission except :

1) In the emergency to protect your rights and welfare.

2) If required by law

AUTHORIZATION TO PUBLISH RESULTS:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with the study and that can be identified with you will remain confidential. Results of the study will be used to improve maternal outcome.

RIGHT TO REFUSE OR WITHDRAW FROM THE STUDY :

You do not have to participate in this research if you do not wish to. You can withdraw at any time from the study. There will be no penalty for withdrawal. Your treatment and care in this hospital will not change irrespective of whether you agree to participate or not. You can be removed from the study if necessary.

Alternative:

You are free to with draw yourself from this study at any point of time. You will continue to receive the routine postnatal care even if you decline to participate in the study. If you develop any adverse effects you will be promptly treated for the same even if you have declined from the study. You will be informed about any new information that may affect your decision to participate in the study.

INSTITUTIONAL/SPONSER'S:

In the event of any injury related to the study, treatment will be made available through KAHER, Belagavi. There is no compensation or payment for such medical treatment by law. If you are injured you may contact **REG NO. BJ0119008HO**, Post graduate student, Department of Obstetrics and Gynaecology, KAHER or by Ph.No:____________.

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CONTACT DETAILS:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact **REG NO. BJ0119008HO**, Post graduate student, department of Obstretics and gynaecology, KAHER, Ph No : __________ or Dr. ______________ (OBG), HOD, Professor, Dept. of Obstetrics and Gynaecology**,** KAHER Belagavi, Ph. No : _________.

If you have any queries about your rights as study participant, you may contact Dr Roopa M Bellad, professor, of paediatrics as chairman of J. N. Medical College institutional ethical Committee on Human subjects Research, Phone no. 0831 2473777 ext- 1527 at J. N. Medical college, Belagavi.

CONSENT STATEMENT:

I, ____ voluntarily agree for participating in the study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read from in my own vernacular language, including the risks and benefits and having all my questions answered.

Participant name : ________________________________

Signature or the left thumb print of participant : _______________

Investigators name: ________________________________ Signature : ________________

Witness Name : ___________________________________ Signature : ________________

Date : ____________

ANNEXURE III - SCREENING FORM.

Screening number:

Date of screening (dd-mm-yyyy) ;

First name: ________________________________

Middle name: ______________________________

Last name: ________________________________

Husband Name: ____________________________

IP Number : ________________________________

Address : H.no: _____________________________

Street: ___________________________

Taluk : ____________________________

District: ___________________________

Phone number : _____________________________

Phone number : _____________________________

Registered	
Unregistered	

ANNEXURE IV– PROFORMA

TITLE: " Efficacy and safety of Ferric Carboxy Maltose in iron deficiency anemia correction in postpartum period"

NAME	
AGE	
ADDRESS	
PHONE NO	
DATE OF ADMISION	
DATE OF DISCHARGE	
IP NO	

OBSTRETIC HISTORY :

GRAVIDA	
PARA	
LIVING	
ABORTION	
STILL BIRTH	

MENSTRUAL HISTORY:

LAST MENSTRUAL PERIOD	
EXPECTED DATE OF DELIVERY	
PERIOD OF GUESTATION	

GENERAL PHYSICAL EXAMINATION :

PULSE RATE	
BLOOD PRESSURE	
PALLOR	
ICTERUS	

PEDAL EDEMA	

SYSTEMIC EXAMINATION:

PER ABDOMEN	
UTERUS	
LOCAL EXAMINATION	

MEAN TOTAL POSTPARTUM BLOOD LOSS :

FETAL OUTCOME - APGAR SCORE :

INVESTIGATIONS :

DATE	
HAEMOGLOBIN	
PERIPHERAL SMEAR	
PCV	
SERUM FERRITIN	

PARAMETERS DURING FCM INFUSSION :

Date :

Weight :

Height :

BMI :

Calculated required dosage :

Dose given :

FCM infusion started at : ______ Completed at : _______

CLINICAL OBSERVATIONS :

	PRE INFUSSION	DURING INFUSSION	POST INFUSSION
GENERAL CONDITION			
PULSE			
BP			
RESP RATE			
TEMP			

ADVERSE EFFECTS :

1	Local reaction	
2	Diarrhoea	
3	Nausea	
4	Vomiting	
5	Pain abdomen	
6	Urticaria	
7	Headache	
8	Hyper/hypotension	
9	Myalgia	
10	Severe anaphylactic reaction	
11	Nil	

TREATMENT GIVEN FOR ADVERSE EFFECT:

ANNEXURE V– KEY TO MASTER CHART

RW	:	Read and Write
PR	:	Primary Schooling
SEC	:	Secondary Schooling
GR	:	Graduation
SES	:	Socio-economic Status
BMI	:	Body Mass Index
FTVD	:	Full Term Vaginal Delivery
FT-EMG LSCS	:	Full Term Emergency LSCS
FT-ELT LSCS	:	Full Term Elective LSCS
PCV	:	Packed Cell Volume
Hb	:	Hemoglobin
PS	:	Peripheral Smear
MICHYPO	:	Microcytic Hypochromic
S/E	:	Side Effects
F/U	:	Follow Up

SR. NO	AGE	SEC	EDUCATION	HEIGHT	WEIGHT	BMI	PARITY	DELIVERY	DATE OF DELIVERY	BLOOD LOSS	HB	PCV	PS	SR. FERRRITIN	IRON DEFICIT	S/E	FCM GIVEN	DATE	F/U DATE	HB ON F/U	% RAISE Hb
1	19	2	RW	160	68	26.5	P1L1	FTVD	07-03-2020	450ML	8.3	23.6	MICHYPO	28.6	1103	NIL	1GM	08-03-2020	04-04-2020	10.2	1.9
2	27	3	PR	154	44	18.5	P2L2	FT-EMG LSCS	03-03-2020	490ML	9.3	27.4	MICHYPO	40.2	785.1	NIL	500MG	02-03-2020	29-03-2020	11.4	2.1
3	25	4	SEC	156	54	22.1	P3L3	FT-EMG LSCS	10-03-2020	450ML	9.8	30.3	MICHYPO	30.2	776.4	NIL	500MG	12-03-2020	20-04-2020	12.4	2.6
4	20	2	SEC	155	57	23.7	PL1	FTVD(V)	09-03-2020	300ML	9.8	25.8	MICHYPO	72.2	800.9	NIL	500MG	11-03-2020	19-04-2020	12	2.2
5	28	3	PR	162	58	22.1	P1L1A1	FT-EMG LSCS	15-09-2020	360ML	9.4	29	MICHYPO	94.2	875.8	NIL	500MG	17-09-2020	10-10-2020	11.2	1.8
6	22	2	SEC	160	52	20.1	P2L2	FT-ELT LSCS	05-03-2020	350ML	9.7	26.7	MICHYPO	94.7	787	NIL	500MG	06-03-2020	25-03-2020	11.8	2.1
7	26	2	SEC	157	72	29.2	P3L2	FT-EMG LSCS	17-09-2020	310ML	9.4	28.9	MICHYPO	16.74	949.2	NAUSEA	1GM	19-09-2020	10-12-2020	12.4	3
8	26	3	RW	154	50	21	P2L2	FT-EMG LSCS	13-09-2020	360ML	10.8	32.2	MICHYPO	87.6	632	NIL	500MG	15-09-2020	10-10-2020	12.9	2.1
9	27	1	GR	167	58	20.8	P1L1	PTVD	15-09-2021	150ML	9.8	26.9	MICHYPO	12.3	716.8	NIL	500MG	16-09-2021	10-11-2021	11.2	1.4
10	23	3	SEC	158	60	24	P1L1	FTVD	04-01-2021	300ML	8.1	24.6	MICHYPO	20.5	1,061.60	NIL	1GM	04-01-2021	22-01-2021	10.2	2.1
11	21	4	RW	152	56	24.2	P1L1	PTVD	03-03-2021	150ML	8.8	27.2	MICHYPO	10.24	930	NIL	1GM	04-03-2021	28-04-2021	10.6	1.8
12	22	4	RW	163	55	20.7	P1L1	FT-EMG LSCS	27-03-2021	300ML	9.7	30.4	MICHYPO	84.7	803.6	NIL	500MG	28-03-2021	26-04-2021	12.1	2.4
13	21	2	SEC	160	58	22.6	P1L0A1	FTVD(MSB)	18-11-2020	420ML	8.9	27	MICHYPO	52.4	931.5	NIL	1GM	20-11-2020	18-12-2020	10.8	1.9
14	27	4	RW	163	44	16.5	P1L1	FT-EMG LSCS	13-09-2021	400ML	10.8	34.2	MICHYPO	13.8	595	NAUSEA	500MG	15-09-2021	05-10-2021	13.2	2.4
15	20	3	SEC	155	48	19.9	P1L1	FT-EMG LSCS	17-12-2020	360ML	9.3	32.5	MICHYPO	95.2	811	NIL	500MG	19-Dec	10-01-2020	11.3	2
16	23	3	SEC	172	70	23.6	P1L1	FT-EMG LSCS	09-01-2021	400ML	9.9	28.2	MICHYPO	30.1	852.8	NIL	1GM	10-01-2021	05-02-2021	12.5	2.6
17	23	1	GR	166	75	27.2	P1L1	FT-EMG LSCS	16-12-2020	360ML	8.5	26.3	MICHYPO	92.5	1130	NIL	1GM	19-12-2020	15-01-2020	10.6	2.1
18	27	3	SEC	168	53	18.7	P2L2	FT-EMG LSCS	25-12-2020	200ML	9	28.7	MICHYPO	73.8	881	NIL	500MG	29-12-2020	20-01-2020	11.6	2.6
19	24	2	SEC	149	52	23.4	P2L2	FT-EMG LSCS	26-12-2020	390ML	9.8	28.8	MICHYPO	40.2	774.5	NIL	500MG	28-12-2020	18-01-2021	12.2	2.4
20	21	4	PR	155	44	18.3	P1L1	FT-EMG LSCS	30-12-2020	380ML	9.3	28.2	MICHYPO	80.6	785	NIL	500MG	01-01-2021	28-01-2021	11.9	2.6
21	24	3	PR	167	60	21.5	P2L2	FT-EMG LSCS	02-01-2021	410ML	10.4	31.9	MICHYPO	42	730	NIL	500MG	04-01-2021	26-01-2021	12.2	1.8
22	25	3	PR	148	46	21	P1L1	PT-EMG LSCS	08-01-2021	220ML	9.2	29.4	MICHYPO	56.4	809.1	NIL	500ML	11-01-2021	05-02-2021	12.1	2.9
23	28	2	GR	156	58	23.8	P2L2A2	FTVD	08-05-2021	200ML	10.8	33	MICHYPO	24.5	625.2	NIL	500ML	10-05-2021	28-05-2021	13.4	2.6
24	24	5	PR	160	52	20.3	P1L1	FTVD	09-05-2021	200ML	8.5	27.9	MICHYPO	64.4	936.8	NIL	1GM	01-05-2021	02-06-2021	10.4	1.9
25	41	4	GR	158	51	20.4	P3L2	FT-EMG LSCS	10-05-2021	380ML	8.5	26.5	MICHYPO	78.2	928.4	NIL	1GM	13-05-2021	08-06-2021	11.2	2.7
26	27	3	SEC	162	58	22.1	P1L1	FT-EMG LSCS	09-12-2020	390ML	8.8	26.2	MICHYPO	25.34	945.44	NIL	1GM	11-12-2020	02-01-2021	11.8	3
27	23	4	PR	167	61	21.8	P1L1A1	FT-EMG LSCS	13-05-2021	350ML	9.2	30.1	MICHYPO		909.9	NIL	1GM	15-05-2021	16-06-2021	11.5	2.3
28	20	3	PR	168	57	20.2	P1L1	FT-EMG LSCS(FSB)	23-05-2021	550ML	7.1	19.7	MICHYPO	18.9	1170.3	NIL	1GM	27-05-2021	21-06-2021	9.8	2.7
29	26	3	PR	157	42	17	P1L1A1	FTVD	25-05-2021	400ML	9	25.4	MICHYPO	12.1	800.4	NAUSEA	500MG	26-05-2021	18-06-2021	10.9	1.9
30	20	2	SEC	160	52	20.3	P1L1	PTVD	28-05-2021	100ML	9	30.6	MICHYPO	32.6	874.4	NIL	500MG	31-05-2021	26-06-2021	11.4	2.4
31	23	3	SEC	157	41	16.6	P1L1	FT-EMG LSCS	30-05-2021	200ML	8.5	28.3	MICHYPO	41.9	844.4	NIL	1GM	01-06-2021	25-06-2021	10.9	2.4
32	21	2	SEC	162	46	17.5	P2L2	FTVD	13-06-2021	150ML	8.9	26.3	MICHYPO	88.4	842.2	NIL	1GM	14-06-2021	02-07-2021	11.3	2.4
33	23	3	PR	159	40	15.8	P2L2	FTVD	14-06-2021	200ML	7.4	22.3	MICHYPO	18.4	941.6	NIL	1GM	15-06-2021	04-07-2021	10.5	3.1

34	23	4	PR	168	62	21.9	P2L2	FT-EMG LSCS	13-06-2021	250ML	8.4	27.4	MICHYPO	28.2	1035.6	HEADACHE	1GM	15-06-2021	04-07-2021	11.6	3.2
35	26	2	SEC	156	42	17.2	P4L4	FTVD	07-06-2021	200ML	10.6	33.8	MICHYPO	84.4	641.1	NIL	500MG	08-06-2021	26-06-2021	12.8	2.2
36	25	4	RW	163	46	17.3	P2L2A2	FT-EMG LSCS	22-06-2021	400ML	9.5	27.8	MICHYPO	30.5	776	NIL	500MG	24-06-2021	15-07-2021	11.4	1.9
37	26	3	SEC	171	66	22.5	P1L1	PT-EMG LSCS	13-01-2021	350ML	9.7	30.4	MICHYPO	46.2	864.3	NIL	1GM	15-01-2021	10-02-2021	12.2	2.5
38	22	2	GR	158	47	18.8	P2L2	FTVD	17-08-2021	80ML	8.5	24.8	MICHYPO	42.8	894.8	NIL	500MG	19-08-2021	15-09-2021	10.8	2.3
39	23	3	PR	152	44	19	P3L3	FTVD	20-11-2020	100ML	9	29	MICHYPO	84.2	816.8	NIL	500MG	21-11-2020	13-12-2020	11.8	2.8
40	21	2	SEC	160	47	18.3	P1L1	FTVD(F)	20-11-2020	300ML	7.1	26.4	MICHYPO	26.4	730.3	NAUSEA	1GM	23-11-2020	20-12-2020	9.2	2.1
41	24	5	RW	158	56	22.4	P1L1	FT-EMG LSCS	23-01-2021	400ML	9.4	29.4	MICHYPO	78.3	645.6	NIL	500MG	25-01-2021	21-02-2021	11.9	2.5
42	20	3	PR	159	60	23.7	P1L1	FTVD(V)	25-05-2020	350ML	8.9	27.4	MICHYPO	24.8	686	MYALGIA	500MG	26-05-2021	14-06-2021	11.3	2.4
43	29	2	SEC	138	40	21	P3L3	FT-ELT LSCS	25-05-2021	350ML	10.6	32.5	MICHYPO	88.2	634.4	NIL	500MG	27-05-2021	18-06-2021	12.4	1.8
44	21	2	GR	158	49	19.6	P1L1	FTVD	22-06-2020	400ML	9.4	29.8	MICHYPO	92.8	805.7	NIL	500MG	23-06-2020	14-07-2020	11.8	2.4
45	20	3	SEC	148	52	23.7	P2L2	FT-EMG LSCS	07-07-2020	500ML	8.9	27.6	MICHYPO	27.6	886.8	NIL	1GM	07-07-2020	28-07-2020	11.3	2.4
46	18	5	RW	168	68	24	P1L1	FTVD	17-08-2020	350ML	8.5	28.2	MICHYPO	23	738	NIL	1GM	19-08-2020	12-09-2020	10.5	2
47	27	2	GR	146	54	25.3	P2L0	PT-EMG LSCS(MSB)	02-01-2021	300ML	9.2	27.8	MICHYPO	27.8	862.8	NIL	1GM	04-01-2021	22-01-2021	11.6	2.4
48	24	3	SEC	161	57	21.9	P1L1	PTVD(V)	02-02-2021	400ML	10.3	32.3	MICHYPO	48.2	732.5	NIL	500MG	03-02-2021	25-02-2021	12.1	1.8
49	30	3	SEC	160	56	21.8	P4L4A1	FTVD	06-02-2021	250ML	10.8	32.7	MICHYPO	98.6	620.9	NIL	500MG	08-02-2021	28-02-2021	12.5	1.7
50	29	2	GR	142	46	22.8	P2L2	FT-ELT LSCS	10-02-2021	230ML	8.4	26.2	MICHYPO	53.6	897.4	NIL	1GM	12-02-2021	28-02-2021	11	2.6
51	22	2	SEC	152	43	18.6	P1L1	PT-EMG LSCS	11-02-2021	330ML	10.8	33.3	MICHYPO	74.1	623.8	NIL	500MG	12-02-2021	28-02-2021	12.2	1.4
52	18	2	SEC	148	53	24.2	P1L1	FTND	10-02-2021	400ML	9.6	29.7	MICHYPO		805.2	NIL	500MG	12-02-2021	28-03-2021	12.2	2.6
53	24	3	PR	157	56	22.7	P4L4	FTVD	24-02-2021	400ML	7.9	24.2	MICHYPO		1051	NIL	1GM	25-02-2021	18-03-2021	9.8	1.9
54	26	3	PR	160	48	18.7	P3L2	FT-ELT LSCS	18-05-2021	450ML	8.8	25.6	MICHYPO		868.6	NIL	1GM	20-02-2021	12-03-2021	11.8	3
55	30	1	GR	170	62	21.4	P2L2	FT-ELT LSCS	06-03-2021	400ML	8.8	26.2	MICHYPO	42.5	976.1	NIL	1GM	08-03-2021	25-03-2021	11.3	2.5
56	30	3	SEC	147	56	25.9	P1L1	FT-EMG LSCS	19-01-2021	300ML	9.8	32.3	MICHYPO	27.2	795.6	NIL	500MG	21-01-2021	14-02-2021	12.3	2.5
57	20	3	SEC	152	50	21.6	P1L1	FTVD	22-06-2021	200ML	10.3	34.1	MICHYPO	67.2	704	HEADACHE	500MG	25-06-2021	15-07-2021	12.5	2.2
58	23	2	SEC	160	57	22.2	P1L1	FTVD(V)	03-03-2020	200ML	8.9	26.2	MICHYPO	22.8	924	NIL	1GM	06-03-2020	09-05-2020	11.2	2.3
59	23	3	SEC	163	61	22.9	P1L1	FTVD	14-03-2020	500ML	8.4	24.5	MICHYPO	78.1	1027	NIL	1GM	16-03-2020	02-04-2020	10.6	2.2
60	29	3	RW	168	58	22.5	P3L3	FT-ELT LSCS	08-10-2020	250ML	9.7	29.2	MICHYPO	34.8	820	NIL	500MG	09-10-2020	28-10-2020	12.4	2.7
61	26	2	PR	170	68	23.5	PL1	FT-EMGLSCS	02-07-2021	300ML	8.9	29.8	MICHYPO	18.6	1005	NIL	1GM	03-07-2021	29-07-2021	11.8	2.9
62	27	3	RW	152	48	20.7	P2L2	FTVD	03-09-2021	400ML	9.8	30.3	MICHYPO	64.6	753.4	VOMITING	500MG	04-09-2021	26-09-2021	11.9	2.1
63	25	3	RW	166	58	21	P2L2A1	FT-ELT LSCS	08-09-2021	440ML	10.8	34.5	MICHYPO	54.5	667	NIL	500MG	09-09-2021	26-09-2021	12.8	2
64	32	5	SEC	162	57	21.7	P1L1	PTVD	14-09-2021	200ML	9.5	30.5	MICHYPO	28.4	856.2	NIL	1GM	15-09-2021	06-10-2021	12.3	2.8
65	23	2	GR	148	48	21.9	P2L2	FTVD	24-11-2019	350ML	10	30.6	MICHYPO	65.7	730.4	NIL	500MG	25-11-2019	15-12-2019	12.3	2.3
66	23	3	SEC	155	53	22	P2L2	PT-EMG LSCS	14-12-2019	310ML	9.5	29.8	MICHYPO	26.8	818	NIL	500MG	15-12-2019	06-01-2020	11.8	2.3
67	23	2	SEC	159	55	21.7	P3L2	FT-ELT LSCS	19-12-2019	360ML	9.3	30.3	MICHYPO	53.2	856.4	NIL	500MG	21-12-2019	12-01-2020	12	2.7
68	25	2	SEC	167	54	19.3	P2L2	FT-EMG LSCS	24-12-2019	370ML	9.4	31.1	MICHYPO	24.9	836.9	NIL	500MG	26-12-2019	16-01-2020	11.8	2.4
69	29	5	RW	148	45	20.5	P1L1A1	PT-EMG LSCS	24-12-2019	360ML	9.1	31.4	MICHYPO	81.9	813.2	NIL	1GM	26-12-2019	18-01-2020	12.1	3

70	21	3	PR	152	52	22.5	P1L1	FT-EMG LSCS	25-12-2019	440ML	8.8	27.4	MICHYPO	35.8	899.3	NIL	1GM	27-12-2019	20-01-2020	10.9	2.1
71	26	5	PR	162	60	22.8	P2L2	FT-EMG LSCS	06-01-2020	400ML	8.7	27.6	MICHYPO	24.7	975.2	NIL	1GM	09-01-2020	24-01-2020	11.2	2.5
72	32	3	PR	154	56	23.6	P1L1	FT-EMG LSCS	08-01-2020	460ML	9	27.3	MICHYPO	44.9	903	NIL	1GM	10-01-2020	28-01-2020	10.7	1.7
73	23	2	SEC	160	58	22.6	P1L1	FT-EMG LSCS	17-01-2020	570ML	8.7	27.7	MICHYPO	68	959.3	NIL	1GM	19-01-2020	12-02-2020	11.2	2.5
74	24	3	GR	156	59	24.2	P3L3	FT-EMG LSCS	21-01-2020	600ml	10.8	33.5	MICHYPO	26.4	669.9	NIL	500MG	24-01-2020	22-02-2020	12.4	1.6
75	19	5	SEC	160	62	24.2	P1L1	FT-EMG LSCS	24-01-2020	300ML	9	28.2	MICHYPO	56.2	946.4	NIL	1GM	26-01-2020	28-02-2020	11.5	2.5
76	25	2	SEC	172	64	21.6	P3L3	FT EMG LSCS	19-02-2020	490ML	9.6	28.5	MICHYPO	46.3	868.6	NIL	1GM	20-02-2020	14-03-2020	11.9	2.3
77	19	3	PR	162	60	22.8	P1L1	FTVD	29-02-2020	200ML	10.3	30.6	MICHYPO	54.2	744.8	NIL	500MG	01-03-2020	22-03-2020	12.4	2.1
78	22	2	PR	148	48	21.9	P2L1D1	PTVD	16-06-2020	450ML	9.7	29.6	MICHYPO	26.9	764.9	MYALGIA	500MG	17-06-2020	08-07-2020	11.9	2.2
79	19	2	SEC	155	53	22	P1L1	PTVD	07-10-2020	150ML	10.2	31.2	MICHYPO	59	728.9	NIL	500MG	08-10-2020	26-10-2020	12.2	2
80	25	3	PR	159	55	21.77	P2L2	FTVD	15-01-2021	200ML	9.4	29.1	MICHYPO	48.2	843.2	NIL	500MG	16-01-2021	12-02-2021	12	2.6
81	26	3	RW	150	54	24	P1L1	FT EMG LSCS	25-08-2020	360ML	9.4	30.1	MICHYPO		836.9	NIL	500MG	26-08-202O	28-09-2020	11.8	2.4
82	30	3	RW	148	52	23.7	P1L1	FT-EMG LSCS	10-09-2020	320ML	10.3	30.2	MICHYPO		712.1	NIL	500MG	12-09-2020	28-10-2020	11.9	1.6
83	26	2	RW	162	59	22.4	P2L2A1	FT-EMG LSCS	10-09-2020	250ML	9	27	MICHYPO		924.8	NIL	1GM	12-09-2020	28-09-2020	10.8	1.8
84	22	1	GR	156	51	20.9	P1L1	FT-EMG LSCS	26-09-2020	500ML	7.9	24.4	MICHYPO	42.8	1001.8	NIL	1GM	28-09-2020	26-10-2020	9.5	1.6
85	28	3	SEC	152	60	25.9	P3L3	PT EMG LSCS	30-09-2020	540ML	8.7	27.6	MICHYPO		975.2	NIL	1GM	03-10-2020	28-10-2020	11.8	3.1
86	24	2	SEC	150	54	24	P1L1	PT-EMG LSCS	03-10-2020	320ML	9.5	28.1	MICHYPO		824	NIL	500MG	05-10-2020	26-10-2020	11.5	2
87	23	5	PR	154	50	21	P2L1	FTVD	27-03-2021	350ML	10	30.2	MICHYPO		740	NIL	500MG	28-03-2021	24-04-2021	12.1	2.1
88	25	2	PR	160	50	19.5	P3L3	FTVD	04-03-2021	150ML	10.2	32.1	MICHYPO		716	NIL	500MG	06-03-2021	07-04-2021	12.5	2.3
89	27	3	PR	168	62	21.9	P3L3	FT-EMG LSCS	23-03-2021	680ML	9.9	29.5	MICHYPO	76.1	630.2	NIL	500MG	26-03-2021	24-04-2021	12.3	2.4
90	20	4	RW	152	48	20.7	P2L1D1	PTVD(MSB)	09-07-2021	150ML	10.3	32.4	MICHYPO	54.3	752.9	NIL	500MG	12-07-2021	29-07-2021	13.4	3.1