Study of FE (III) Hydroxide Polymaltose Complex to Correct Anemia in Cancer Patients

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A B S T R A C T

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Introduction: Anemia of cancer is characterized by ineffective erythropoiesis, which is due to a number of factors. One of the most important among these is abnormal iron metabolism. There is also 'functional failure' due to retention of iron in macrophages. Hence iron supplementation forms an important part for the treatment of anemia in cancer patients. Oral iron supplements, usually in the form of ferrous (Fe^{2+}) salts, are toxic to the gastrointestinal mucosa, leading to intolerance, resulting in poor compliance and failure of treatment. The sugar derivative maltose strongly chelates iron, and stabilizes in the less toxic ferric (Fe^{3+}) form. This chelated form of iron shows high bioavailability which eliminates the need for frequent dosing and therefore improves compliance. **Materials and Method:** This was a prospective, single centred, open label, non-randomised study involving 20 patients of whom 17 completed the study. The patients were treated with ferric hydroxide polymaltose complex syrup (50mg/5ml) for 8 weeks. **Results:** At the end of 8 weeks, there was a significant increase in haemoglobin of the patients (from 9.41±1.24 to 10.92±0.91 g/dL, mean±s.d. P < 0.0001, paired t-test, t = 7.065, df = 16, confidence interval - 0.05.). Out of 17, 7 patients i.e. 41.18% showed a ⩾ 2 g/dl rise in hemoglobin during or at the end of the treatment. Mean time required to achieve this rise in hemoglobin is found to be 7 weeks. **Conclusion:** The results demonstrate that Fe (III) hydroxide polymaltose complex is effective in improving hemoglobin levels in anemic cancer patients.

Keywords: Anemia, Iron deficiency anemia, Anemia of Cancer, Fe (III) Hydroxide Polymaltose complex,

INTRODUCTION

Anemia is the most common hematologic abnormality in patients with cancer. Cancer and its treatments impair erythropoiesis. Cancer can disturb erythrocyte production by directly affecting the bone marrow (e.g., infiltration of the tumour cells into the bone marrow), blunting the erythropoietin response, and reducing the synthesis and release of endogenous erythropoietin. Cancer and its treatment may also result in the development of nutritional deficiencies that can lead to the development of anemia.[1]

Cancer-related anemia most closely resembles the anemia of chronic disease. In anemia of chronic disease, cytokines alter iron homeostasis, erythroid progenitor cell proliferation, and erythropoietin production, all of which contribute to its pathogenesis.[2] Proinflammatory states can affect erythropoiesis by stimulating the production of cytokines that can cause erythroid progenitor cell damage, reduce erythropoietin production, inhibit the release of iron from iron stores, and decrease duodenal iron absorption.[3] The discovery of hepcidin, an iron regulatory peptide produced by the liver, has improved the understanding of anemia associated with cancer and other chronic inflammatory states.[4]

Hepcidin inhibits iron transport across cell membranes, decreases available iron from iron stores, and reduces gastrointestinal absorption of dietary iron by inactivating the only known exporter of iron, ferroportin. Hepcidin is upregulated in most chronic inflammatory conditions and cancer. Upregulation of hepcidin results in the sequestration of iron in macrophages, reduction of iron levels in plasma due to decreased absorption from the intestinal epithelium, and a restricted delivery of iron to erythroid marrow. The result is the development of iron-restricted erythropoiesis, or functional iron deficiency.[5]

Iron replacement therapy is essential for replenishing iron stores and raising hemoglobin levels in patients with Iron deficiency anemia, regardless of the etiology. Generally the oral iron therapy is preferred and is considered to be safe as compared to IV or IM administration. For iron replacement therapy 60-120 mg of elemental iron per day is given usually as three or four iron tablets (each containing 50 to 65 mg elemental iron) given over the course of the day.[6]

In addition to iron supplementation, treatment of Iron Deficiency Anemia (IDA) may include blood transfusion and for some patients ESA (erythropoesis stimulating agent therapy). Blood transfusions are not without risk; the most

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serious of which are transmission of infectious diseases (hepatitis, HIV etc.), allergic reactions, haemolytic reactions and circulatory overload. In addition it may also lead to iron overload when performed for a prolonged period of time. ESA therapy can also be effective in raising hemoglobin levels, but it also increases the requirement for iron.[7]

Various studies have shown that absorption of Fe (III) polymaltose complex is greater than that of ferrous salts. This occurs with significantly less gastrointestinal side effects from the former. In the longer term there is a theoretical benefit of protecting individuals from atherogenic effects of iron salts, thought possibly to be mediated by lipid peroxidation due to oxidative stress.[8] Maltol itself may delay recycling of Fe^{3+} to Fe^{2+} and hence when re-expansion of body iron stores is considered, the complex has advantages in that tolerance is better than with sulphate salt.[9]

Interestingly, iron has a number of other interactions with cytotoxic chemotherapy and may produce free-radical oxidative injury that appears related to the structure of the compound administered. These observations initiated studies to define alternative formulations such as linking ferric moiety to sugars resulting in an iron polymaltose complex.[10] Nevertheless, there is preliminary data suggesting that oral supplementation with ferrous sulphate may increase susceptibility of plasma lipoproteins to oxidation, and this is not found with non-ionic iron polymaltose complex. Furthermore, the later formulation is equivalent in correcting haemoglobin levels, and doing so without gastrointestinal toxicity with polymaltose may provide a more physiologic approach to replacement therapy.[10]

It is possible that such a formulation is handled by enterocytes in the same way as dietary iron, thereby explaining relative lack of toxicity. An extrapolation of this hypothesis is that it may offer a solution to supplementation. Thus ferric polymaltose could provide a less toxic alternative to ferrous salts in the oral treatment of iron-deficiency.[10]

MATERIALS AND METHOD

Study Design: This was a prospective, single center, open label, non-randomized study. The study was carried out at Cancer Department, Shree Krishna Hospital, Karamsad.

Study approval: Human research ethics committee (HREC) approval was obtained in September 2011 from the HREC of Shree Krishna Hospital, Karamsad.

Methodology:

- Patients were screened and recruited according to the inclusion and exclusion criteria.

- Hematological tests are routinely carried for cancer patients undergoing chemotherapy. From these tests, hemoglobin and MCV of the patients were taken into consideration while screening. Patients with Hemoglobin < 13 g/dL in men and < 12 g/dL in women and MCV < 80 fl were further screened for Serum iron levels and Total Iron Binding Capacity (TIBC)

- Serum iron and TIBC (Total Iron Binding capacity) were obtained by carrying out laboratory tests. Using these values the TSAT (Transferrin Saturation) of the patients was calculated using following formula:

$$TSAT = \frac{(Serum\ iron* 100)}{TIBC}$$

- Informed consent of each patient was taken after the screening procedure. Total treatment period was of 8 weeks

- Drug used for treatment in this study was Fe (III) hydroxide polymaltose complex syrup (50mg/5ml). The prescribed dose is 5 ml of syrup once daily. The drug was given to the patients for a period of 8 weeks after which Hemoglobin and MCV of the patients were recorded

Study End-points:

Primary end point: Proportion of subjects achieving a ⩾ 2.0g/dl increase in hemoglobin at any time from baseline to 8 weeks

Secondary end-point: Mean change in hemoglobin of all the patients from base line to 8 weeks

Patient selection criteria:

Inclusion criteria:

- Patients with age ⩾ 18 years, both genders included

- Subjects with Iron deficiency anemia defined as:

  a) Hemoglobin < 13 g/dL in men and <12 g/dL in women

  b) MCV < 80 fl

  c) TSAT < 30%

- Patients with non-hematological cancer and currently on cancer chemotherapy

- Patients capable of understanding and complying with the protocol requirements and available for the duration of the study

Exclusion criteria:

- History of allergy to iron

- Subjects on dialysis or with an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2

- Patients with serum ferritin > 600 ng/ml

- Erythropoesis-stimulating agent (ESA) therapy initiated, stopped or dose changed by >20% within 4 weeks prior to screening

Statistical analysis: The data obtained at baseline and follow-up were analyzed using paired t-test with the help of Graph Pad Prism 5 software.

RESULTS

Total 22 patients were screened for iron deficiency, of which 20 patients were found to be iron deficient and were recruited in the study. Of these 20 patients, two of the patients passed away during the study period and one patient showed a decline in general condition leading to failure in follow up. Therefore the total patient population at the end of the study was 17.

Table 1: Base-line characteristics:	
Characteristic	**Mean± S.D. (N=17)**
Age (yrs)	49.70±12.40
Body Weight (Kg)	47.75±10.31
Hemoglobin (g/dl)	9.40±1.24
MCV (fl)	75.15±7.88
Serum iron (mg/dl)	48.99±27.14
TIBC (mg/dl)	324.55±77.24
TSAT (%)	15.41±0.09

Follow-up data:

Hemoglobin of all the patients was recorded at the follow-up. Hemoglobin values of all the patients at baseline and after 8 weeks of treatment are depicted in the table 2.

Primary end point:

Primary end point of the study was to check the proportion of subjects achieving a ≥ 2.0g/dl increase in hemoglobin at any time from baseline to 8 weeks and to calculate mean time required to achieve that.

From the above data (table 2), it is found that 7 out of 17 patients i.e. 41.18% of the patients showed a ≥ 2 g/dl rise in hemoglobin during or at the end of the treatment. Mean time required to achieve this rise in hemoglobin was found to be 7 weeks.

Secondary end point:

Secondary end point was to calculate mean change in hemoglobin of all the patients from base line to 8 weeks. From table 2 it has been found that mean change in hemoglobin of the patients after the treatment of 8 weeks with the drug is

Table 2: Follow up data			
Patient No.	Hemoglobin at baseline (g/dl)	Hemoglobin after 8weeks) (g/dl)	Rise in hemoglobin (g/dl)
1	9.9	11.9	2.0
2	9.3	11.7	2.4
3	10.9	12.8	1.9
4	10.7	11.6	0.9
5	8.9	10.6	1.7
6	9.09	10.2	1.11
7	8.1	10	2.1
8	9.8	10	0.2
9	8.6	10.6	2.0
10	10.6	11.2	0.6
11	7.4	10	2.6
12	8.8	10.7	1.9
13	8.5	11.4	2.9
14	10.7	10.9	0.2
15	11	12	1.0
16	7.2	9.3	2.1
17	10.7	10.8	0.1
Mean±sd	**9.41±1.24**	**10.92±0.91**	**1.5±0.87**

1.5±0.87. At the end of 8 weeks, there was a significant increase in haemoglobin (from 9.41±1.24 to 10.92±0.91 g/L, mean±s.d. P < 0.0001, paired t-test, t = 7.065, df = 16, at a confidence interval of 0.05.) of the patients treated with ferric hydroxide polymaltose complex. [Paired t-test carried out using Graph pad prism 5 software]. The data is shown in the form of following graph.

Fig.1: Hemoglobin (mean±s.d.) levels before and after the treatment with ferric hydroxide polymaltose complex
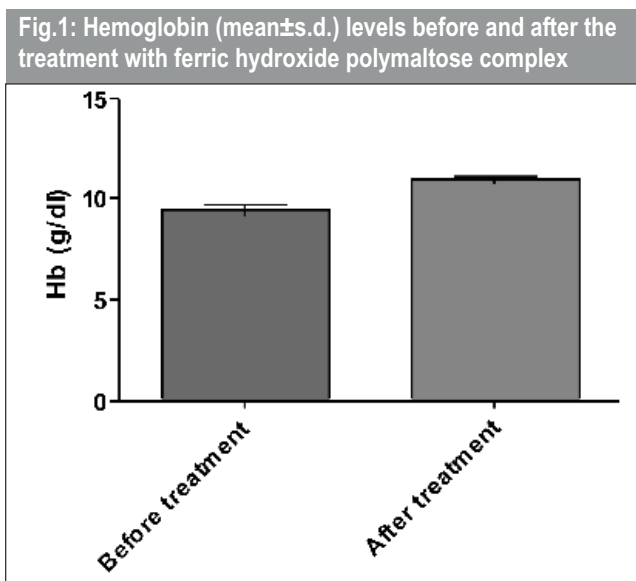
There were no serious adverse events recorded during the study. Only 2 out of 17 patients had complained of constipation initially, but that was resolved after 2 weeks without any specific treatment for constipation.

DISCUSSION

The results obtained from this prospective, single centre, open label, non-randomized study of 17 patients treated with Ferric hydroxide polymaltose complex syrup (50 mg/5ml) showed a significant increase in hemoglobin levels of the patients after a treatment of 8 weeks.

A number of previous studies have indicated prevalence iron deficiency anemia in cancer patients and have emphasized on the need to correct iron deficiency in these patients as a part of the treatment of anemia.[11, 12] In the present study, a total of 22 patients were screened, of which 20 were found to be Iron deficient. This coincides with the previous studies and depicts the prevalence of iron deficiency anemia among cancer patients.

The treatment of iron deficiency anemia (IDA) is directed at replenishing hemoglobin and compensating for the deficit in stored iron by supplying sufficient iron. The iron polymaltose complex has been formulated in such a way that the elemental iron is in non-ionic state. This ensures that there is no gastric irritation with iron polymaltose complex. In addition, the high elemental iron content of iron polymaltose complex eliminates the need for frequent dosing and therefore improves compliance.[13] These results have been shown in the previous studies carried out by Beril Yasa et al[14], K. Erichson et al[15] and R.S.J. Harvey et al[16] which concluded that ferric polymaltose complex is effective in correcting iron deficiency anemia with lower incidence of side effects. However, these studies were carried out on different population groups which included pregnant women, paediatric patients and patients with Anemia of chronic disease (inflammatory bowel disease and cancer).

At the end of the study, 7 patients (41.18%) showed a $\geq$ 2 g/dl rise in hemoglobin level. From the remaining 10 patients, 5 showed a rise in hemoglobin that was found to be significant, and rest 5 patients who did not show a significant rise in hemoglobin were found to be actively bleeding (Hematemesis, hematuria and occult GI bleeding that was attributed to their neoplastic disease). These responses were achieved with remarkably few side-effects. These coincide with the previous findings[71-75] and suggest that ferric hydroxide polymaltose complex could be of benefit in treatment of anemia in cancer patients.

CONCLUSION

It can be concluded from this study that Ferric hydroxide polymaltose complex is effective in treatment of anemia in cancer patients, undergoing chemotherapy. After a treatment of 8 weeks with the drug (dose 50 mg/5 ml), patients have shown a significant rise in hemoglobin level without any serious side effects of the drug.

However, this study has certain drawbacks such as: has small sample size and is an open label study. But positive results pave a pathway for further studies and larger trials to establish the role of ferric hydroxide polymaltose complex in the treatment of anemia in cancer patients.

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