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PARENTERAL VERSUS ORAL IRON THERAPY FOR THE PREVENTION AND TREATMENT OF CANCER CHEMOTHERAPY INDUCED ANAEMIA

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ABSTRACT

Background: Head and neck cancers are among the 10 most frequent cancers in the world. During treatment of cancer patients with chemotherapy, schedule of chemotherapy is disturbed by development of chemotherapy induced anaemia which necessitates the supplementation of iron that can be given orally or parentally. **Objective:** The aim of this study was to evaluate and compare the effects of parenteral iron vs oral iron in the prevention and treatment of cancer chemotherapy induced anaemia. **Methods:** This was a prospective, randomized, comparative, open label, parallel study conducted on 60 patients having histopathologically proven head and neck squamous cell carcinoma. In this study 60 treatment naïve patients of head and neck cancer were divided in two groups, parenteral iron and oral iron group. The effects of treatment were compared using various parameters such as hemoglobin, RBC count, reticulocyte count, peripheral blood films and red cell indices. **Results**: The results showed that parenteral iron led to lesser fall in hemoglobin, reticulocyte count, MCV, MCH, MCHC, PCV and RBC count as compared to oral iron, less incidence of anaemia at 3 weeks which was more evident at 6 weeks. **Conclusion:** This study showed that cancer chemotherapy led to anaemia in all patients and supplementation of iron along with cancer chemotherapy had a preventive as well as therapeutic effect on chemotherapy induced anaemia. Parenteral iron provided more benefit as compared to oral iron.

KEYWORDS: Cancer, chemotherapy, oral iron, parenteral iron.

INTRODUCTION

Cancer is a disease characterized by the uncontrolled growth and spread of abnormal cells.[1]Head and neck cancers are among the 10 most frequent cancers in the world.[2] Chemotherapy has different types of role in different cases of cancer.[3] Drugs like platinum compounds, fluorouracil etc. have been used concomitantly with radiation therapy to increase the local control and survival in head and neck cancer patients.[4]

Cancer chemotherapy leads to bone marrow suppression leading to anaemia.[5] Majority of cancer patients have anaemia at presentation & several factors may induce or exacerbate the condition e.g.tumour type, disease stage, duration, intensity and type of treatment.[6]

Treatment with erythropoiesis stimulating agents (ESAs) increases haemoglobin concentration in some anaemic cancer patients.[7] However, in 2008, clinical trials of ESAs in cancer patients have confirmed that patients who received ESAs for anaemia had 17% higher on-study mortality than those treated with blood transfusions alone.[8] Intravenous iron (IV Fe) is beneficial in chemotherapy-induced anaemia (CIA) but because of the clinical nature of adverse events associated with it, it is under- used.[9] Randomised clinical trials have shown superior efficacy of i.v. iron over oral or no iron in reducing blood transfusions, increasing haemoglobin.[10]

This study was planned in view of the fact that the completion of chemotherapy is essential for better cure rate but sometimes is not possible because of cancer chemotherapy induced anaemia. Intravenous iron (IV Fe) therapy is the latest recommended care in cancer chemotherapy induced anaemia as it increases hematopoietic responses. So, the role of intravenous iron as compared to oral iron, in prevention and treatment of anaemia in head and neck cancer patients receiving combination chemotherapy was studied.

MATERIAL AND METHODS

A prospective, randomized, comparative, open label, parallel study was conducted by the Departments of Pharmacology and Radiotherapy, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak on 60 patients of either sex having histopathologically proven head and neck squamous cell carcinoma, where definitive treatment had been decided as neoadjuvant chemotherapy. An informed consent was obtained from all patients enrolled for the study. All the baseline investigations required for cancer chemotherapy were done (liver function tests, renal function tests and X-ray chest). A total of

60 patients of either sex, divided in two groups of 30 patients each were randomly allocated to receive two different routes of administration of iron therapy for the prophylaxis and treatment of cancer chemotherapy induced anaemia. The patients having Hb 12-13 were taken for preventive purpose and patients having Hb 8-11.9 were taken for curative purpose. The patients were screened and head and neck squamous cell carcinoma patients who were suitable for neoadjuvant chemotherapy having complete haemogram with Hb 8-13gm/dL, TLC > 4000/mm^3, Platelet count > 100,000/mm^3 were included in the study.The patients having any of the following conditions were excluded from the study i.e. who had prior radiation, surgery or chemotherapy for the disease, histopathology other than squamous cell carcinoma, distant metastasis, pregnant or lactating females, age less than 14 years, history of allergy to iron, associated medical condition such as renal disease, liver disease or heart disease.

All the patients received a combination chemotherapy regimen consisting of Inj. Docetaxel 80mg/m^2, Inj. Carboplatin 300mg/m^2, and Inj. 5-fluorouracil 600mg/m^2, every 3 weekly for 3 courses (i.e. at 0, 3 & 6 weeks).

The patients were randomly assigned to one of the two groups and received parenteral iron in the form of Injection Iron Sucrose 200 mg IV weekly for six weeks in group 1 and oral iron was given as ferrous ascorbate tablets 200 mg daily in two divided doses to group 2 patients. The treatment was given for six weeks along with 3 courses of combination chemotherapy.

The assessment was carried out in all the patients in terms of efficacy of the treatment. The patients were assessed every week for six weeks to see the status of anaemia by observing haematological investigations. The Primary end points of the study were haemoglobin (Hb), Peripheral blood film (PBF) and Reticulocyte count. Secondary end points were Mean corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration (MCHC), Packed cell volume (PCV) and Red blood cells (RBC) count. Hb, MCV, MCH, MCHC, PCV and RBC count were assessed by cell counter method.

RESULTS

In group I, the age of the patients ranged from 37 years to 74 years of age (mean 55.90±1.99) and in group II this range was from 37 to 65 years (mean 55.13±1.42). The difference between age of the patients was statistically insignificant ($p < 0.742$). Sex distribution was

same in both the groups i.e. 2 females and 28 males out of the total of 30 patients in each group.

Assessment of parameters: The various parameters of anaemia were assessed at the time of presentation (0 week) and then weekly up to 6 weeks in both the groups. The mean of the individual values are given in Table-1. Comparison of the baseline values in both the groups shows that all the parameters of the two groups were comparable at the time of admission. This shows that at the time of recruitment of the patients in the study, all of them had almost similar values of various hematological parameters and the variation in baseline readings did not have any bearing on the outcome of the study.

TABLE 1

HAEMATOLOGICAL PARAMETERS ASSESSMENT IN PARENTERAL VS ORAL IRON THERAPY

	Parameter	Baseline value	3 weeks	6 weeks
Group I (Parenteral iron group)	Hemoglobin	12.14±0.12	10.94±0.14***	10.33±0.14***###
	Reticulocyte count	1.64±0.16	1.23±0.11***	0.99±0.09***###
	MCV	90.23±1.08	85.86±1.06***	81.81±1.14***###
	MCH	29.22±0.57	28.35±0.54***	27.43±0.62***###
	MCHC	32.75±0.25	31.59±0.23***	30.79±0.30***###
	PCV	43.66±0.89	41.36±0.83***	39.63±0.80***###
	RBC count	4.26±0.15	3.92±0.12***	3.66±0.12***###
Group II (Oral iron group)	Hemoglobin	12.17±0.16	10.25±0.18***$$	9.59±0.16***###@@
	Reticulocyte count	1.54±0.15	1.05±0.90***	0.75±0.07***###@
	MCV	89.94±1.06	82.43±1.16***$	75.84±1.25****###@@
	MCH	29.97±0.36	27.10±0.24***$	25.44±0.32***###@
	MCHC	32.37±0.22	30.89±1.37***$	29.91±0.24****###@
	PCV	42.35±0.81	39.06±0.66***$	36.31±0.59***###@@
	RBC count	4.42±0.90	3.62±0.09***$	3.32±0.97***###@

Intragroup analysis

**Comparison of baseline values with values after 3rd and 6th week of treatment in both the groups*

#Comparison of 3rd week values with values after 6th week of treatment in both the groups

/#→p<0.05, **/##→p<0.01, */###→p<0.001*

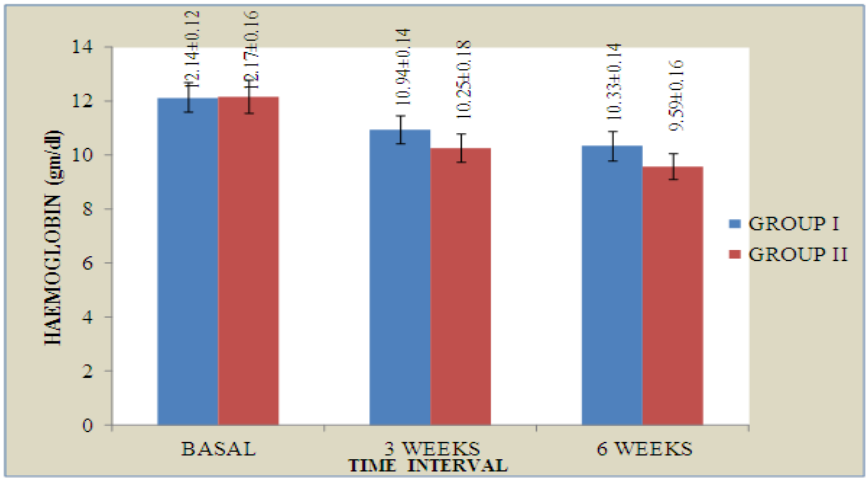
Intergroup analysis

$---comparison between value of group I and group II at 3 weeks

@--- comparison between value of group I and group II at 6 weeks

$/@→p<0.05, $$/@@→p<0.01, $$$/@@@→p<0.001

Figure 1



COMPARISON OF HAEMOGLOBIN VALUES IN BOTH THE GROUPS

TABLE 2 INCIDENCE OF HYPOCHROMIC/MICROCYTIC ANAEMIA IN BOTH THE GROUPS

	Parameter	Basal	3 weeks	6 weeks
Group I	Hypochromic/microcytic	2	5	12
Group II	Hypochromic/microcytic	2	8	19

Group I- Parenteral iron receiving patients

Group II- Oral iron receiving patients

Intragroup analysis

**Comparison of baseline values with values after 3rd and 6th week of treatment in both the groups*

#Comparison of 3rd week values with values after 6th week of treatment in both the groups

/#→p<0.05, **/##→p<0.01, */###→p<0.001*

Intergroup analysis

$---comparison between value of group I and group II at 3 weeks

@--- comparison between value of group I and group II at 6 weeks

$/@→p<0.05, $$/@@→0.01, $$$/@@@→p<0.001

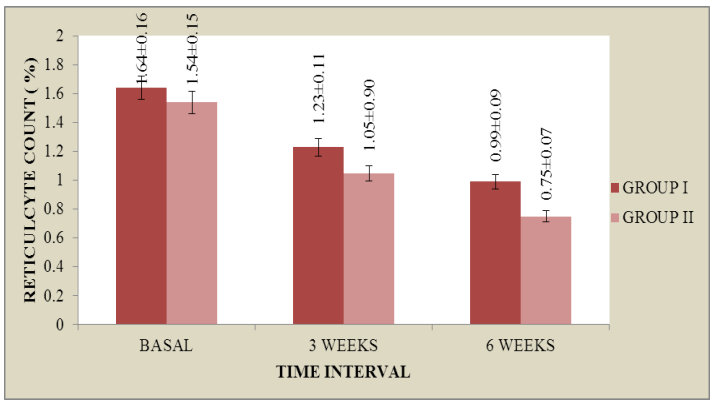
Hemoglobin: There was statistically significant decrease in haemoglobin in both the groups. The mean value of haemoglobin (gm/100ml) at base line, after 3 weeks and after six weeks

respectively in Parentral iron group and Oral iron group were as follows: base line- 12.14 vs 12.17, at 3 weeks 10.94 vs 10.25, at 6 weeks 10.33 vs 9.59. When both the groups were compared with each other at 3 weeks (10.94 vs 10.25, p *<0.01*) and 6 weeks (10.33 vs. 9.5, p *<0.01*), statistically significant difference was seen and more fall in haemoglobin levels was seen with oral iron group as shown in Table-1 and Figure-1.

Reticulocyte count

There was statistically significant decrease in reticulocyte count in both the groups. The mean value of reticulocyte count (%) at base line, after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: base line- 1.64 vs 1.54, at 3 weeks 1.23 vs 1.05, at 6 weeks 0.99 vs 0.75.When both the groups were compared with each other at 3 weeks (1.23 vs 1.05), no statistical difference was noted whereas at 6 weeks (0.99 vs 0.75, p *<0.05*), statistically significant difference was seen and more fall in reticulocyte count levels was seen with oral iron group as shown in Table-1 and Figure-2.

FIGURE 2



COMPARISON OF RETICULOCYTE COUNT IN BOTH THE GROUPS

RBC: There was statistically significant decrease in RBC count in both the groups. The mean value of RBC count (million/microlitre) at base line, after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: base line- 4.26 vs 4.42, at 3 weeks 3.92 vs 3.62, at 6 weeks 3.66 vs 3.32.When both the groups were compared with each other at 3 weeks (3.92 vs 3.62, p *<0.05*) and 6 weeks (3.66 vs 3.32, p *<0.05*), statistically significant difference was seen and more fall in RBC count was seen with oral iron group as shown in Table-1.

MCV/MCH/MCHC/PCV

MCV: There was statistically significant decrease in MCV in both the groups. The mean value of MCV (gm/dl) at base line, after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: base line-90.23 vs 89.94, at 3 weeks 85.86 vs 82.43, at 6 weeks 81.81 vs 75.84.When both the groups were compared with each other at 3 weeks (85.86 vs 82.43, p *<0.05*) and 6 weeks (81.81 vs 75.84, p *<0.01*), statistically significant difference was seen and more fall in MCV levels was seen with oral iron group as shown in Table-1.

MCH: There was statistically significant decrease in MCH in both the groups. The mean value of MCH (pgm) at base line, after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: base line-29.22 vs 29.97, at 3 weeks 28.35 vs 27.10, at 6 weeks 27.43 vs 25.44.When both the groups were compared with each other at 3 weeks (28.35 vs 27.10, p *<0.05*) and 6 weeks (27.43 vs 25.44, p *<0.05*), statistically significant difference was seen and more fall in MCH levels was seen with oral iron group as shown in Table-1.

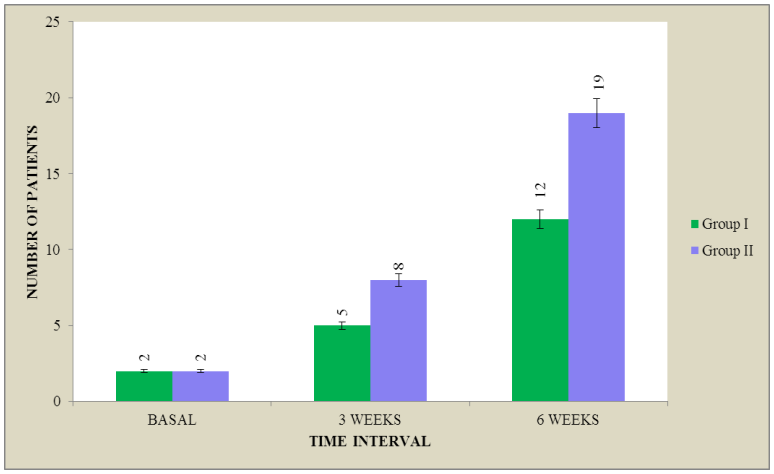
MCHC: There was statistically significant decrease in MCHC in both the groups. The mean value of MCHC (gm/100ml) at base line, after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: base line- 32.75 vs 32.37, at 3 weeks 31.59 vs 30.89, at 6 weeks 30.79 vs 29.91.When both the groups were compared with each other at 3 weeks (31.59 vs 30.89, p *<0.05*) and 6 weeks (30.79 vs 29.91, p *<0.05*), statistically significant difference was seen and more fall in MCHC levels was seen with oral iron group as shown in Table-1.

PCV: There was statistically significant decrease in PCV values in both the groups. The mean value of PCV (%) at base line, after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: base line- 43.66 vs 42.35, at 3 weeks 41.36 vs 39.06, at 6 weeks 39.63 vs 36.31.When both the groups were compared with each other at 3 weeks (41.36 vs 39.06, p *<0.05*) and 6 weeks (39.63 vs 36.31, p *<0.01*), statistically significant difference was seen and more fall in PCV was seen with oral iron group as shown in Table-1.

Peripheral blood film (PBF) There was increase in number of patients having hypochromic microcytic anaemia in both the groups. The number of patients having hypochromic

microcytic anaemia in both the groups at base line was 2 whereas the incidence after 3 weeks and after six weeks respectively in Parentral iron group and Oral iron group were as follows: at 3 weeks 5 vs 8 patients, at 6 weeks 12 vs 19 patients.When both the groups were compared with each other at 3 weeks (5 vs 8 patients) and 6 weeks (12 vs 19 patients), no statistically significant difference was seen on chi square test as shown in Figure-3.

FIGURE 3



COMPARISON OF INCIDENCE OF HYPOCHROMIC/MICROCYTIC ANAEMIA IN BOTH THE GROUPS

DISCUSSION

Haemoglobin: Haemoglobin is the important parameter to measure iron deficiency anaemia. Our study revealed that both the groups showed significant decrease in haemoglobin values after chemotherapy. The comparison between the two groups revealed that chemotherapy induced fall in haemoglobin was more in oral iron group as compared to the parenteral iron group and this difference was statistically significant. The study conducted by Dangsuwan and Manchana also showed a significant fall in haemoglobin due to chemotherapy in both parenteral as well as oral iron group which was more in oral iron group.[11] Another study conducted by Kim et al showed that the requirement of blood transfusion was in 40% of the patients in parenteral iron treated group as compared to 60% in oral iron treated group. Moreover the oral iron group received more transfusion volume than the parenteral iron group in each chemotherapy cycle.[12] Henry et al also showed that increase in mean haemoglobin in anaemic cancer patients receiving chemotherapy and epoetin alpha, was more for parenteral iron (ferrous gluconate), than oral iron or no iron.[13] Gafter-Gvili et al conducted a meta-analysis of eleven trials including 1681 patients, the majority examining

the role of IV iron. IV iron significantly increased haematopoietic response by a factor of 1.28 and decreased the rate of blood transfusions to 52%. The increase in haematopoietic response rate correlated with total IV iron dose, regardless of baseline iron status.[14] Thus the results of our study are in accordance with the results of these studies.

Reticulocyte count & RBC count: Reticulocyte count and RBC count are also good parameters to measure iron deficiency anaemia. Effective erythropoiesis is most simply estimated by determining the reticulocyte count. Reticulocytosis (an increased number of peripheral blood reticulocytes) occurs in iron deficiency anemic patients with a functional bone marrow, whereas anaemic patients with a dysfunctional bone marrow produce decreased numbers of reticulocytes, and have decreased numbers of peripheral blood reticulocytes (i.e., reticulocytopenia).[15]Anaemia is functionally defined as an insufficient RBC mass to adequately deliver oxygen to peripheral tissues.[16]

The present study revealed that both the groups showed significant decrease in reticulocyte count and RBC count after chemotherapy. The comparison between the two groups revealed that decrease was more in oral iron group than parenteral iron group and the difference was statistically significant. A study conducted by Follézou and Bizon on patients with advanced solid malignancies also showed that after chemotherapy there was decrease in reticulocyte count.[17] The probable mechanism for the constant reduction in reticulocyte count is because of impairment of the bone marrow function leading to dysfunctional erythropoiesis, due to anticancer drugs.

MCV, MCH, MCHC & PCV: MCV, MCH & MCHC are collectively known as red cell indices. These are also important diagnostic tools for measuring iron deficiency anaemia. The MCV tends to be the single most useful measurement. The MCV and MCH almost always correlate closely.[18]As the iron deficiency worsens, a mild normochromic, normocytic anaemia often develops. With further progression, haemoglobin concentration, erythrocyte count, mean corpuscular volume (MCV), and mean erythrocyte haemoglobin (MCH) all decline together. This decrease in MCV, MCH and MCHC manifests as hypochromic microcytic picture in blood.[16] Packed cell volume (PCV) is another significant parameter for assessment of iron deficiency anaemia.

This study revealed that both the groups showed significant decrease in MCV, MCH, MCHC & PCV values after chemotherapy.The comparison between the two groups revealed that

decrease in these values caused by chemotherapy induced anaemia was more in oral iron as compared to parenteral iron and this difference was statistically significant.

The study conducted by Dangsuwan and Manchana also showed a significant fall in PCV values due to chemotherapy in both parenteral as well as oral iron group. The findings of our study are in accordance to the findings of this study.[11]

Peripheral blood film (PBF): Peripheral blood film is another important parameter to measure iron deficiency anaemia. With the development of iron deficiency anaemia, the peripheral blood smear reveals the appearance of microcytic cells. With more severe anaemia (haemoglobin7–8 g/dL), peripheral blood smear reveals hypochromia and microcytosis. Our study revealed that both the groups showed increase in the incidence of hypochromic microcytic blood film after chemotherapy. However, the comparison between the two groups showed no statistically significant difference.

CONCLUSION

This study which was conducted on head and neck cancer patients, showed that cancer chemotherapy led to anaemia in all the patients and supplementation of iron along with cancer chemotherapy had a preventive as well as therapeutic effect on chemotherapy induced anaemia. Parenteral iron provided much more benefit as compared to oral iron as evident by various parameters like haemoglobin, reticulocyte count, RBC count, MCV, MCH, MCHC, PCV and peripheral blood film.

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