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Efficacy and Safety of Nutritional Supplements Versus Ferrous Sulfate in Managing Anemia in Head and Neck Cancer Survivors: A Randomized Clinical Study

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ABSTRACT

In this randomized clinical trial, 100 anemic head and neck cancer survivors in the form of two groups-A & B, each with 50 patients) were assigned to receive nutritional supplement (Group A) and a standard ferrous sulfate (Group B) daily for 30 days. Hemoglobin levels, liver and kidney function tests (LFT, KFT), and imaging studies were assessed at multiple time points. Statistical analysis was performed using SPSS. A p-value < 0.05 was considered significant.

Keywords: Head and Neck cancer, Anemia, Nutritional supplements, Ferrous sulfate, Hemoglobin, Clinical trial.

INTRODUCTION

Anemia is a prevalent and clinically significant sequela among survivors of head and neck squamous cell carcinoma (HNSCC), particularly following cytotoxic chemoradiotherapy[9-11]. Its etiology is multifactorial, involving direct myelosuppressive effects of chemotherapy, radiation-induced marrow damage, inflammation-driven hepcidin dysregulation, and nutritional deficiencies. Anemia in this population is associated with diminished radiosensitivity, increased tumor hypoxia, impaired functional recovery, and reduced overall survival and quality of life[1,2].

Oral ferrous sulfate remains a standard intervention for chemotherapy-induced iron deficiency anemia (IDA). However, its therapeutic utility is frequently constrained by gastrointestinal intolerance, low compliance, and potential hepatotoxicity, especially in cancer survivors with compromised systemic reserves[3,4]. In addition, inflammation-mediated iron sequestration and hepcidin overexpression may limit the bioavailability of orally administered iron, rendering traditional monotherapy insufficient in functionally iron-deficient patients[5].

Some people are using nutritional supplements that include bioavailable iron from plants as well as vitamin C, folic acid and vitamin B[12]. Products rich in phytonutrients including those

made from Moringa oleifera and Spirulina platensis help regulate immunity and defend against free radicals which may help prevent complications in people receiving cancer treatment[6,7]. Also, vitamin C increases non-heme iron absorption in the intestine, while folate and cobalamin are important additions to DNA synthesis during the growth of red blood cells[8].

Even though these iron salts make sense clinically and their use is rising, few studies have compared them directly to standard iron salts in people with cancer[12-14]. As anemia can develop for post-treatment head and neck cancer survivors, the current study investigated the hematological benefits, protection against hepatic and renal problems and impact on radiographs when using ferrous sulfate or a plant-based supplement[24].

MATERIALS AND METHODS

The study protocol pertains to the research sanctioned by the Drug Controller General of India (DCGI) under protocol number 10/ECJKCI/2024.

Study Design and Population

This open-label, randomized controlled trial enrolled 100 patients (n=50 in each group) aged 40–70 years, with a history of head and neck cancer, completed primary treatment >1 year prior, and diagnosed with anemia (Hb<12 g/dL).

Inclusion and Exclusion Criteria

Inclusion: Completed cancer treatment, hemoglobin <12 g/dL, age 40–70 years.

Exclusion: Chronic kidney or liver disease, recent transfusions, comorbidities affecting iron metabolism.

Intervention

Group A received a daily nutritional supplement containing 15 mg plant-based iron, 75 mg vitamin C, 400 mcg folic acid, 1 mcg B12, Moringa, and Spirulina. Group B received 200 mg ferrous sulfate (65 mg elemental iron).

Assessments

Hemoglobin, Liver Function Tests (LFT)-Alanine transaminase (ALT), Aspartate transaminase (AST), Kidney Function Tests -KFT (creatinine, urea, eGFR), and radiological exams (X-ray and CT-scan) were recorded on Day 1, 7, 14, and 30.

Statistical Analysis

Data were analyzed using SPSS. Shapiro-Wilk test checked normality. Intergroup comparisons used unpaired t-tests; intragroup changes used paired t-tests. One-way ANOVA analyzed longitudinal data. Significance set at $p<0.05$.

RESULTS

Hemoglobin Response Over Time

Both treatment groups exhibited a progressive increase in hemoglobin concentrations over the 30-day study period as shown in the Fig. 1. In Group A, hemoglobin levels rose from 10.2 ± 0.8 g/dL at baseline to 11.3 ± 0.7 g/dL on Day 7, 12.0 ± 0.6 g/dL on Day 14, and 12.8 ± 0.5 g/dL by Day 30. In contrast, Group B demonstrated a less pronounced increase, with hemoglobin values rising from 10.1 ± 0.9 g/dL at baseline to 10.7 ± 0.8 g/dL on Day 7, 11.1 ± 0.7 g/dL on Day 14, and 11.4 ± 0.6 g/dL at the end of the study.

Statistically significant differences in hemoglobin levels between the two groups were observed starting from Day 7 ($p<0.05$), becoming more pronounced by Day 14 ($p<0.01$), and reaching high statistical significance by Day 30 ($p<0.001$). The rate and magnitude of hemoglobin recovery were consistently greater in Group A, suggesting superior efficacy of the nutritional supplement over standard iron therapy.

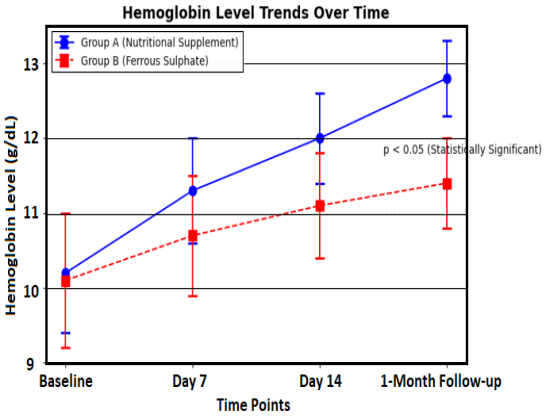

Fig. 1. Hemoglobin levels trends over time

Liver Function Test (LFT) Parameters

Liver function parameters were measured at the end of the study (Day 30) to assess the hepatotoxic potential of both treatments (Fig. 2). Group A maintained stable hepatic enzyme levels with ALT at 29 ± 5 U/L and AST at 27 ± 4 U/L, and total bilirubin at 0.8 ± 0.1 mg/dL. In contrast, Group

B showed elevated enzyme levels with ALT at 44 ± 6 U/L, AST at 40 ± 5 U/L, and bilirubin at 1.1 ± 0.2 mg/dL. These differences were statistically significant ($p<0.05$), indicating a mild hepatic burden associated with ferrous sulfate therapy that was not observed with the nutritional supplement.

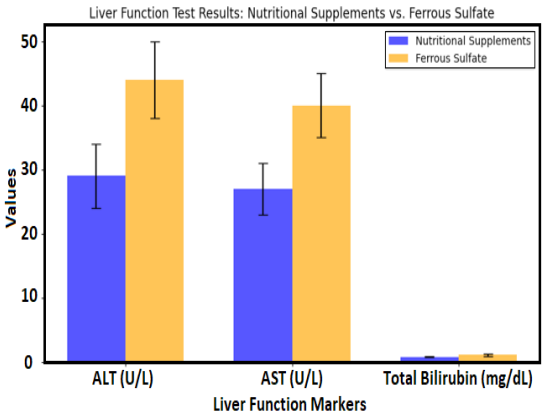

Fig. 2. LFT results for nutritional and ferrous sulfate

Kidney Function Test (KFT) Parameters

Renal function was also evaluated on Day 30. As presented in Fig. 3 Group A exhibited stable renal parameters, with serum creatinine at 0.9 ± 0.1 mg/dL, urea at 26 ± 3 mg/dL, and an eGFR of 90 ± 5 mL/minute. Conversely, Group B presented signs of mild renal impairment with serum creatinine at 1.2 ± 0.2 mg/dL, urea at 34 ± 4 mg/dL, and a reduced eGFR of 78 ± 6 mL/minute. The intergroup differences in all parameters were statistically significant ($p<0.05$), suggesting that ferrous sulfate may exert a mild nephrotoxic effect not seen with the nutritional supplement.

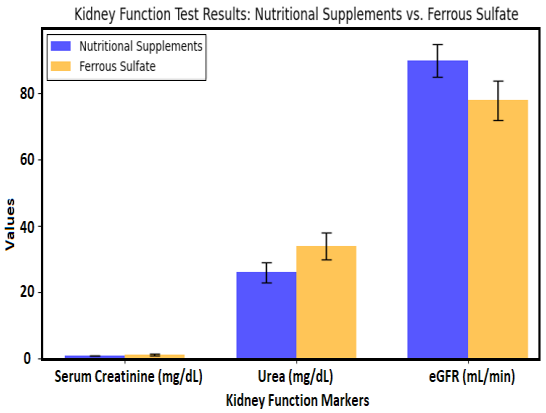

Fig. 3. KFT results for nutritional and ferrous sulfate

Radiological Assessment

Radiological evaluations were performed to monitor any disease progression or systemic effects[15]. CT scans in both groups showed no evidence of tumor recurrence or new lesions.In the report of CT scan the soft tissue density space occupying mass lesion in posterior. Lesion is also involving right side of soft plate and lateral oropharyngeal walls. Fibrofatty planes between hyoid bone and epiglottis are lost. Bone integrity was preserved in the majority of patients[16,17]. However, X-ray findings revealed mild osteopenia in 10% of patients in Group B, potentially indicating subclinical micronutrient imbalance or iron overload due to ferrous sulfate. No such findings were noted in Group A.

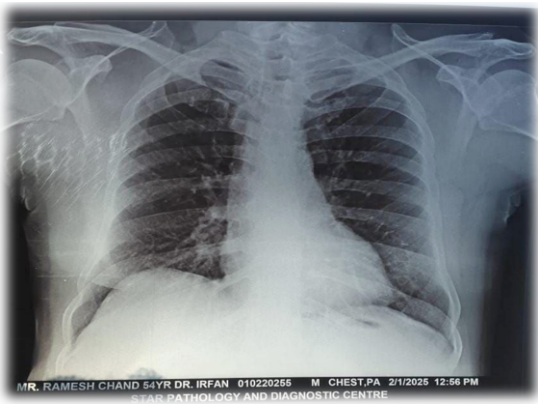

Fig. 4. Radiological evaluations using X-rays

Summary of Statistical Analysis

Shapiro-Wilk tests confirmed the normal distribution of hemoglobin data[18] in both groups, validating the use of parametric tests as shown in Fig. 5. Unpaired t-tests revealed significant between-group differences in hemoglobin at all time points from Day 7 onwards (Fig. 6). Paired t-tests within each group confirmed significant hemoglobin increases over time. One-way ANOVA showed highly significant temporal changes in hemoglobin for both groups (Group A: $F=792.02$, $p< 0.0001$; Group B:$F=272.96$, $p<0.0001$), with greater effect size and consistency in Group A.

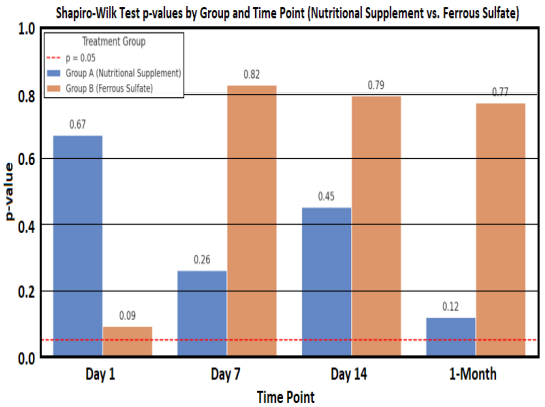

Fig. 5. Distribution of hemoglobin data by Shapiro-Wilk tests

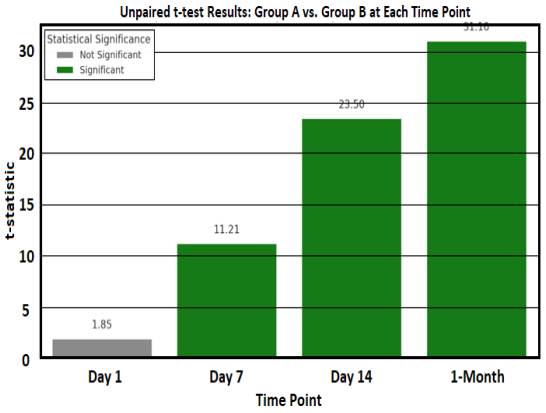

Fig. 6. Unpaired t-tests results

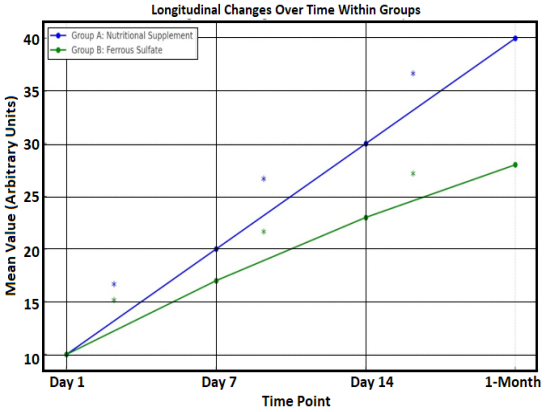

Fig. 7. Paired t-tests within each group

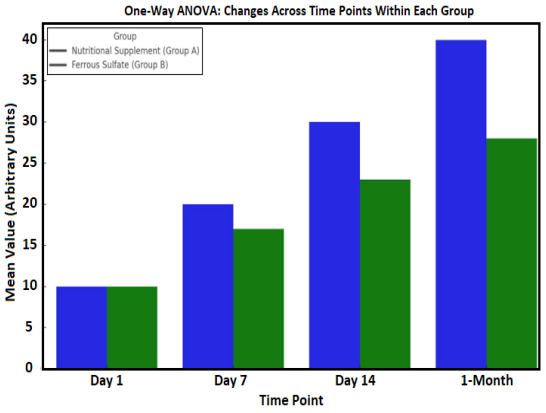

Fig. 8. One-way ANOVA analysis

DISCUSSION

This randomized clinical study compared the efficacy and safety of a plant-based nutritional supplement to standard ferrous sulfate in the management of anemia among head and neck cancer survivors. The findings demonstrate that the nutritional supplement not only led to a significantly greater and more consistent increase in hemoglobin levels but also exhibited superior hepatic and renal safety profiles.

The hemoglobin trajectory observed in Group A, which received the nutritional formulation, revealed a steady and statistically significant improvement from baseline to Day 30. This suggests enhanced iron utilization, possibly attributed to the synergistic action of plant-based elemental iron, vitamin C, folic acid, and vitamin B12. Vitamin C enhances non-heme iron absorption by reducing ferric to ferrous iron in the gastrointestinal tract, while folate and B12 are essential for DNA synthesis in rapidly proliferating erythroid progenitors. The inclusion of Moringa oleifera and Spirulina platensis, both known for their high bioavailable iron content and antioxidant properties, may further contribute to the observed hematological response by mitigating oxidative stress-induced erythrocyte damage-a common phenomenon in cancer survivors' post-chemotherapy or radiotherapy[7,8].

In contrast, although Group B (ferrous sulfate) showed a rise in hemoglobin levels, the magnitude and rate of increase were comparatively blunted. This is consistent with prior literature noting that ferrous sulfate, while effective, is often limited by poor bioavailability and gastrointestinal side effects that reduce adherence[4]. Additionally, functional iron deficiency due to inflammation-mediated hepcidin upregulation in cancer patients may limit the release of iron from stores, further compromising the effectiveness of ferrous salts[5].

Beyond hematologic response, the hepatic and renal safety profiles markedly favored the nutritional supplement. Mild elevations in ALT, AST, and serum creatinine observed in the ferrous sulfate group, though clinically manageable, reflect a potential subclinical burden on hepatic and renal systems[23]. This is particularly relevant in cancer survivors with comorbidities or residual organ vulnerability post-treatment. The stability of these parameters in Group A underlines the tolerability and systemic safety of the nutritional approach, making it more suitable for long-term use in this population.

Radiological assessments, while not the primary endpoint, provided reassuring evidence of oncologic stability, with no signs of recurrence or metastasis in either group. Interestingly, incidental

findings of mild osteopenia in 10% of patients in Group B may be related to iron-induced oxidative stress or micronutrient imbalance, supporting the need for a more holistic approach to supplementation in cancer care[2].

The findings of this study are aligned with emerging perspectives in supportive oncology care, which advocate for integrated, nutrient-based therapies tailored to the metabolic and physiological needs of cancer survivors. While intravenous iron and erythropoiesis-stimulating agents remain options,[19,20] they are resource-intensive and carry notable risks. A safe, effective, and orally bioavailable alternative like the nutritional supplement studied here could serve as a first-line or adjunctive treatment, particularly in outpatient survivorship clinics.

However, the study is not without limitations. The relatively short duration of follow-up (30 days) may not capture long-term outcomes, such as sustained hemoglobin correction or delayed adverse effects. Because serum ferritin, transferrin saturation and hepcidin levels are absent, it is difficult to understand the mechanisms at work[21,22]. Even so, the open-label style can result in some bias, though scientists attempt to hide the analysis.

Yet, the similarity in results among hematological, biochemical and imaging parameters suggests that supplementation is better than ferrous sulfate in this case. Because of these findings, better anemia management protocols in oncology should focus on what is best for the patient, safety and their quality of life.

CONCLUSION

The study clearly demonstrated that using a plant-based supplement instead of ferrous sulfate gives better and safer results for people dealing with anemia after head and neck cancer surgery. People who took the nutritional supplement showed a higher and faster rise in hemoglobin, along with a safe profile for their liver and kidneys. Instead, using ferrous sulfate could cause liver and kidney markers to go slightly higher and infection might show up in images.

The nutritional intervention works well due to its broad composition which contains non-heme iron, along with hematopoietic cofactors such as vitamin C, folic acid and vitamin B12, plus antioxidant botanical components such as Moringa and Spirulina. This way of thinking addresses lack of iron and also the many causes of anemia found in cancer survivors such as inflammation, excessive stress and nutritional deficiencies.

Because they work well, are safe for most patients and encourage compliance, nutritional supplements are a suitable initial or additional therapy for anemia in people who have had cancer. The results emphasize that we should reconsider our methods for treating anemia and add micronutrient-based formulas to the usual care after cancer treatment.

In future, more extensive research should involve multiple centers' participation, continue monitoring for longer and incorporate iron function biomarkers, scores for quality of life and cost analyses to support these findings. Individualized care plans focused on nutrition may reshape how cancer survivors receive support, allowing them to do better while also dealing with fewer treatment side effects.

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Conflict of interest

No conflict of interest among all the authors.

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