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Original Research

Effectiveness of Iron and ESA Therapy in Chronic Disease-Associated Anemia: A Prospective Analysis

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ABSTRACT

Background: Anemia associated with chronic inflammation, commonly referred to as Anemia of Chronic Disease (ACD), frequently occurs in individuals with persistent inflammatory disorders. It is primarily characterized by diminished iron availability for erythropoiesis and suboptimal red blood cell production. The therapeutic goal in ACD management includes optimizing hemoglobin concentration, mitigating clinical manifestations, and enhancing patient well-being. This investigation was undertaken to assess and contrast the therapeutic effectiveness of iron therapy versus erythropoiesis-stimulating interventions in individuals with ACD.

Materials and Methods: A randomized, controlled clinical study was carried out involving 120 adult subjects confirmed to have ACD. The cohort was randomly assigned into two treatment arms. Group A (n=78) was administered oral elemental iron at a dosage of 100 mg per day for a total of 12 weeks. Group B (n=78) received subcutaneous injections of epoetin alfa, 40,000 IU, once weekly for the same treatment period. Hemoglobin concentration, serum ferritin, and transferrin saturation (TSAT) were recorded at the outset, mid-point (6 weeks), and conclusion (12 weeks) of the study.

Results: After 12 weeks of treatment, elevation in hemoglobin was significantly greater in Group B when compared to Group A ($p<0.01$). Serum ferritin levels increased in both the groups. Transferrin saturation improved across both arms, with Group A demonstrating a more marked enhancement. No major adverse events were identified during the course of the trial.

Conclusion: The administration of erythropoiesis-stimulating agents proved more effective in elevating hemoglobin levels than oral iron therapy alone in patients with Anemia of Chronic Disease. However, iron supplementation yielded a comparatively greater effect on transferrin saturation. Continued investigation is warranted to assess the long-term outcomes and safety of these treatment strategies.

Key Words: Anemia, Iron, Erythropoietin, Chronic disease

INTRODUCTION

Anemia associated with chronic illnesses, also known as anemia of inflammation, is frequently observed in clinical settings and is typified by disrupted red blood cell production and altered iron handling. It is commonly linked to prolonged inflammatory states, persistent infections, autoimmune disorders, and malignancies. Distinct from iron deficiency anemia, this condition is characterized by normal or increased iron stores within the body, but with limited bioavailability for erythropoiesis, a result of pro-inflammatory mediators that interfere with both iron mobilization and erythropoietin synthesis [1-3].

The underlying mechanisms involve elevated circulating hepcidin, a peptide hormone that inhibits the release of iron from macrophages and suppresses gastrointestinal iron uptake, culminating in a state of functional iron restriction despite sufficient total body

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iron. Inflammatory molecules such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) further hinder erythropoietic responses by blunting the action of erythropoietin, thereby worsening anemia [4-6].

Therapeutic strategies for managing anemia of chronic disease primarily focus on improving hemoglobin levels, enhancing patient well-being, and reducing dependence on blood transfusions. Standard interventions include iron therapy, administered either orally or via parenteral routes, to restore iron balance and stimulate red cell production. However, persistent inflammation often limits the effectiveness of this approach by impairing iron uptake and utilization [7,8].

To address these limitations, erythropoiesis-stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa, have been introduced to promote red cell generation and elevate hemoglobin concentrations through direct stimulation of bone marrow erythropoietic activity. Nonetheless, the clinical use of ESAs is not without risk, as these agents have been linked to adverse outcomes, including thrombotic complications and increased cardiovascular events [9,10].

Comparative analyses exploring the therapeutic benefits of iron supplementation versus ESA therapy in anemia of chronic disease have yielded inconsistent findings. While some investigations report better hemoglobin correction with ESA administration, others highlight the necessity of adequate iron availability to optimize treatment response [11-13]. The absence of a universally accepted management protocol underscores the need for continued research.

The current investigation seeks to evaluate and compare the therapeutic outcomes of iron therapy and ESA administration in patients with anemia of chronic disease by analyzing changes in hemoglobin concentration, serum ferritin levels, and transferrin saturation across a 12-week observational period.

MATERIAL AND METHODS

A randomized clinical investigation was undertaken to evaluate and compare the effectiveness of iron therapy and erythropoiesis-stimulating medications in the treatment of ACD. The study population consisted of 156 adult individuals (aged ≥18 years) who were diagnosed with ACD based on clinical assessment and laboratory parameters, including hemoglobin concentrations below 11 g/dL, serum ferritin levels above 100 ng/mL, and transferrin saturation values below 20%. Subjects presenting with iron-deficiency anemia, hematologic cancers, ongoing blood loss, or poorly controlled systemic illnesses were excluded from participation. Informed written consent was obtained from all eligible participants prior to their inclusion in the study.

Eligible subjects were randomly distributed into two intervention groups using a computer-generated randomization protocol:

- Group A (Iron Therapy): Participants received oral elemental iron at a dosage of 100 mg per day over a 12-week period.
- Group B (ESA Treatment): Participants were administered subcutaneous injections of epoetin alfa, dosed at 40,000 IU once weekly for 12 weeks.

Assessments were carried out at three time points—initial visit (baseline), midpoint (6 weeks), and study conclusion (12 weeks). Each visit involved a clinical examination along with relevant laboratory investigations to determine both the therapeutic efficacy and safety profile of the respective interventions.

The primary efficacy endpoint was the alteration in hemoglobin levels from the start of treatment to the 12-week mark. Secondary outcome variables included variations in serum ferritin concentrations and transferrin saturation (TSAT).

- Hemoglobin: Quantified using an automated hematology analyzer.
- Serum Ferritin: Measured using enzyme-linked immunosorbent assay (ELISA) methodology.
- TSAT: Derived from the formula: (Serum Iron ÷ Total Iron-Binding Capacity) × 100.

Potential adverse effects linked to the interventions were continuously monitored throughout the study duration. Participants were instructed to report any symptoms or undesirable effects as they occurred.

Statistical analyses were carried out using SPSS software, version 22.0. Continuous variables were described using means and standard deviations. Between-group comparisons were evaluated using independent-samples t-tests, while within-group differences were analyzed using paired-samples t-tests. For comparisons involving more than two datasets, one-way analysis of variance (ANOVA) was employed. A p-value below 0.05 was considered to indicate statistical significance.

RESULTS

In the baseline profile of the study groups (Table 1), both Group A (Iron) and Group B (ESA) were comparable in terms of age, gender distribution, hemoglobin, serum ferritin, and transferrin saturation (TSAT). The mean age of Group A was 54.1 ± 12.1 years, while Group B had a slightly higher mean age of 57.2 ± 11.3 years, although this difference was not statistically significant ($p = 0.67$). The gender distribution was also similar between the groups, with Group A consisting of 42 males and 36 females, and Group B consisting of 39 males and 39 females ($p = 0.45$). Additionally, the baseline values for hemoglobin, serum ferritin, and TSAT were almost identical in both

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groups, with no significant differences ($p = 0.53$, $p = 0.63$, and $p = 0.74$, respectively).

Table 1: Baseline profile of study groups

Variables	Group A (Iron) (n = 78)	Group B (ESA) (n = 78)	p-value
Age; in years	54.1 ± 12.1	57.2 ± 11.3	0.67
Gender (Male/Female)	42 / 36	39 / 39	0.45
Hemoglobin (gm/dL)	9.3 ± 0.8	9.5 ± 0.7	0.53
S. Ferritin (ng/mL)	82.1 ± 10.0	78.5 ± 10.3	0.63
TSAT (%)	17.0 ± 3.1	17.8 ± 3.4	0.74

Table 2 presents a comparison of the hematological variables between the two groups at different time points. Regarding hemoglobin levels, both groups showed significant improvements from baseline to 12 weeks. At 6 weeks, Group A showed a slight increase in hemoglobin to 10.2 ± 0.7 g/dL, while Group B showed a greater increase to 11.1 ± 0.8 g/dL ($p < 0.01$). This trend continued at 12 weeks, with Group A reaching a mean of 10.5 ± 0.9 g/dL and Group B achieving 12.0 ± 1.0 g/dL, again with a significant difference ($p < 0.01$).

In terms of serum ferritin, both groups showed increases over time. At 6 weeks, Group A had a mean serum ferritin of 101.0 ± 11.2 ng/mL, while Group B had 99.5 ± 10.7 ng/mL, with no significant difference between the two groups ($p = 0.41$). However, by 12 weeks, Group A's serum ferritin had risen to 118.0 ± 12.5 ng/mL, while Group B's increased to 114.0 ± 11.9 ng/mL, with a statistically significant difference observed ($p < 0.05$).

For TSAT, both groups showed increases over time. At 6 weeks, Group A's TSAT improved to 22.0 ± 2.8%, while Group B's TSAT was 21.0 ± 3.0%, with a significant difference between the groups ($p < 0.05$). By 12 weeks, Group A had a TSAT of 24.3 ± 3.0%, while Group B had 23.0 ± 3.2%, again with a statistically significant difference ($p < 0.05$).

Table 2: Comparison of Hematological Variables between study groups

Variables	Group A (Iron) (n = 78)	Group B (ESA) (n = 78)	p-value
Hemoglobin (gm/dL)			
Baseline	9.3 ± 0.8	9.2 ± 0.7	-
At 6 Weeks	10.2 ± 0.7	11.1 ± 0.8	<0.01
At 12 Weeks	10.5 ± 0.9	12.0 ± 1.0	<0.01
Serum Ferritin (ng/mL)			
Baseline	81.5 ± 10.0	80.0 ± 9.8	-
At 6 Weeks	101.0 ± 11.2	99.5 ± 10.7	0.41
At 12 Weeks	118.0 ± 12.5	114.0 ± 11.9	<0.05
TSAT (%)			
Baseline	17.0 ± 3.2	17.4 ± 3.5	-
At 6 Weeks	22.0 ± 2.8	21.0 ± 3.0	<0.05
At 12 Weeks	24.3 ± 3.0	23.0 ± 3.2	<0.05

DISCUSSION

Anemia in chronic inflammatory states is predominantly driven by restricted iron utilization and suppressed endogenous erythropoietin activity, mediated by pro-inflammatory cytokines including IL-6 and TNF-α [4,6]. These inflammatory signals induce hepatic hepcidin production, which limits intestinal iron uptake and promotes sequestration of iron within macrophages, thereby reducing systemic availability [5]. The present study observed that the group receiving iron therapy demonstrated notable improvements in TSAT and ferritin concentrations, indicative of partial reversal of functional iron restriction [8].

The marked elevation in hemoglobin values among individuals treated with ESAs corresponds with prior literature demonstrating that these agents augment erythropoiesis by promoting the proliferation and maturation of erythroid progenitor cells [7,10]. The increase in hemoglobin in the ESA group aligns with outcomes from earlier research that reported similar hematologic benefits with epoetin alfa administration [9,11,13].

Nonetheless, iron supplementation remains an essential aspect of therapy, particularly in cases where TSAT is markedly reduced. Although oral iron has shown effectiveness in improving iron indices, its bioavailability is often compromised by elevated hepcidin levels and limited gastrointestinal absorption in the context of chronic inflammation [12,14]. In this study, the iron-treated cohort showed a moderate hemoglobin increment, suggesting that improved iron utilization occurred despite the inflammatory environment.

A noteworthy observation was the variation in ferritin values between the two treatment arms at the conclusion of the follow-up period. As an acute-phase reactant, ferritin tends to be elevated during systemic inflammation, reducing its specificity as a marker of true iron stores in patients with chronic disease-related anemia [15,16]. Nonetheless, the

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increase in ferritin within the iron-treated group implies enhanced iron availability and storage, which may support erythropoietic recovery.

This study's limitations include the relatively brief follow-up duration and the exclusion of intravenous iron administration, which may have demonstrated superior effectiveness compared to oral formulations in the inflammatory setting of ACD. Furthermore, long-term safety profiles associated with ESA therapy were not assessed, underscoring the need for extended evaluation. Future research should aim to assess the efficacy of combination regimens involving both iron therapy and ESAs, and also investigate emerging therapeutic agents such as hepcidin inhibitors and hypoxia-inducible factor (HIF) stabilizers, which hold promise for enhancing systemic iron availability and stimulating erythropoiesis through alternative pathways.

CONCLUSION

The findings of this study indicate that the use of ESAs was significantly more effective in increasing hemoglobin concentrations in patients diagnosed with ACD compared to oral iron supplementation alone. This suggests that ESAs play a more direct role in stimulating red blood cell production, especially in the context of chronic inflammation, where iron utilization is often impaired. The accelerated hematologic response observed with ESA therapy highlights its potential clinical utility in improving oxygen-carrying capacity and alleviating anemia-related symptoms more rapidly.

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