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Comparative study of tolerance and efficacy of conventional iron therapies in iron deficiency anemia: A prospective observational analysis

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Abstract
Background: Iron deficiency anemia (IDA) is a common global health issue characterized by low hemoglobin levels due to insufficient iron. Conventional oral iron supplements such as Ferrous Fumarate, Ferrous Ascorbate, and Ferrous Pyrophosphate are commonly prescribed, yet their comparative efficacy and tolerability remain underexplored.
Objective: This study aimed to compare the tolerance and efficacy of Ferrous Fumarate, Ferrous Ascorbate, and Ferrous Pyrophosphate in the treatment of IDA.
Methods: A prospective observational study was conducted over three months with 99 patients diagnosed with IDA, divided into three groups: Group A (Ferrous Fumarate), Group B (Ferrous Ascorbate), and Group C (Ferrous Pyrophosphate). Hemoglobin levels were measured at baseline, 1 month, 2 months, and 3 months. Tolerance was assessed based on patient-reported symptoms and clinical observations. Statistical analyses were performed using SPSS version 23.0.
Results: Group B (Ferrous Ascorbate) exhibited the most significant and sustained increase in hemoglobin levels, from 10.7±0.8 g/dL at baseline to 11.3±0.8 g/dL at 3 months ($p < 0.05$). Group C (Ferrous Pyrophosphate) also showed significant improvement but reported higher incidences of tiredness and shortness of breath. Group A (Ferrous Fumarate) showed an initial increase in hemoglobin, but this improvement was not sustained, resulting in a non-significant overall change ($p > 0.05$).
Conclusion: Ferrous Ascorbate demonstrated superior efficacy in improving hemoglobin levels compared to Ferrous Fumarate and Ferrous Pyrophosphate. However, Ferrous Pyrophosphate's side effects warrant consideration. The choice of iron supplement should balance efficacy with patient tolerability. Future research should focus on long-term effects, adherence, and broader population studies to refine treatment strategies for IDA.

Keywords: Iron deficiency anemia, ferrous fumarate, ferrous ascorbate, ferrous pyrophosphate, iron supplements, hemoglobin levels, efficacy, tolerability, comparative study

Introduction
Iron deficiency anemia (IDA) is a widespread global health issue, affecting millions of people, particularly women and children. It is characterized by a reduction in the number of red blood cells or hemoglobin concentration due to insufficient iron levels [1]. Iron is essential for numerous physiological functions, including oxygen transport, DNA synthesis, and cellular metabolism. Its deficiency impairs these critical processes, leading to symptoms such as fatigue, weakness, and decreased quality of life [2].
Iron deficiency can arise from various causes, including inadequate dietary intake, impaired absorption, or increased loss due to conditions like gastrointestinal bleeding or menstruation. In response to iron deficiency, oral iron supplements are commonly prescribed to replenish iron stores and improve hemoglobin levels. Among the conventional iron supplements, ferrous fumarate, ferrous sulfate, and ferrous gluconate are widely used. Each form has distinct properties affecting its absorption, efficacy, and tolerability [3].
The efficacy of these iron supplements can be influenced by factors such as dosage, bioavailability, and patient compliance. Additionally, side effects such as gastrointestinal discomfort, nausea, and altered taste can impact patient adherence to therapy [2]. Despite the availability of various iron supplements, there is limited research comparing their relative efficacy and tolerability in a systematic manner.

Understanding the comparative efficacy and tolerability of different iron supplements is crucial for optimizing treatment strategies for IDA. This study aims to address this gap by evaluating and comparing the effects and side effects of ferrous fumarate, ferrous ascorbate, and ferrous pyrophosphate in patients with IDA. By providing insights into which supplements offer the best balance of effectiveness and tolerability, this research seeks to guide clinicians in making informed decisions to improve patient outcomes and adherence to iron therapy.

Methodology

This prospective observational study was conducted over a three-month period at PSG Hospitals, Coimbatore, within the Departments of General Medicine and Obstetrics and Gynaecology. The study was approved by the Institutional Human Ethics Committee (IHEC, PSG IMSR) under Project No. 23/024. Adult patient aged 18 years and older with hemoglobin levels between 5.0 and 10.0 g/dl were eligible to participate, provided they could give informed consent and adhere to follow-up requirements. Patients with liver, renal, or bleeding disorders, or those with anemia due to causes other than iron deficiency, were excluded. A total of 99 patients were enrolled after random allocation into three groups: Group A received ferrous fumarate, Group B received ferrous ascorbate, and Group C received ferrous pyrophosphate. Each supplement was administered according to standard dosage guidelines over the three-month study period. Baseline demographic and clinical data were collected prior to intervention, with follow-up assessments at one-month intervals to evaluate changes in hemoglobin levels and monitor tolerance. Hemoglobin was measured at baseline and at each follow-up visit using standard laboratory techniques. Tolerance and side effects were monitored through patient self-reports and clinical observation, focusing on symptoms such as fatigue, shortness of breath, weakness, skin pallor, brittle nails, dizziness, altered taste, gastrointestinal discomfort, and pain. Statistical analysis was performed using SPSS version 23.0, with descriptive statistics for baseline and follow-up data, and comparative analyses using Student's t-test and ANOVA. Incidence of side effects among groups was compared using chi-square tests, with a significance threshold set at $p < 0.05$. Follow-up evaluations were conducted at one-month intervals throughout the study to assess patient responses and tolerability to the prescribed iron supplements.

Results

Out of the 99 patients enrolled in the study, 33 were assigned to Group A (Treated with Ferrous fumarate), 33 to Group B (Treated with Ferrous ascorbate), and 33 to Group C (Treated with Ferrous pyrophosphate). Table 1 presents the age distribution of the study participants across the three groups. Group a (Ferrous fumarate) and Group B (Ferrous ascorbate) have a similar age distribution, with the majority of participants aged between 18 and 29 years. In contrast, Group C (Ferrous pyrophosphate) includes a wider age range, with a notable proportion of participants in the older age brackets (40-79 years). The mean age of participants in Group A was 28±4.9 years, in Group B was 27.7±3.6 years, and in Group C was significantly higher at 41.5±17.7 years. This demographic variation is important for interpreting the study's findings, as age-related factors can influence treatment responses and tolerance.

Table 1: Study population age characteristics

Age (in years)	Group A (n=33)	Group B (n=33)	Group C (n=33)
18-29	22	23	12
30-39	10	10	6
40-49	1	0	5
50-59	0	0	4
60-69	0	0	3
70-79	0	0	3
Mean± SD	28±4.9	27.7±3.6	41.5±17.7

Table 2 shows the sex distribution of the study participants across the three groups. Group A (Ferrous fumarate) and Group B (Ferrous ascorbate) each consisted entirely of female participants, with 33 females in each group. Group C (Ferrous pyrophosphate) included 4 male participants and 29 female participants. This distribution highlights the gender composition in each treatment group, which is important for understanding the generalizability of the study results.

Table 2: Study population sex characteristics

Sex	Group A (n=33)	Group B (n=33)	Group C (n=33)
Male	0	0	4
Female	33	33	29

The effectiveness of the three different iron supplements was assessed by measuring hemoglobin levels at four intervals: baseline (Before), 1 month (Review 1), 2 months (Review 2), and 3 months (Review 3). The results for each group are summarized in Table 3.

In group A, hemoglobin levels increased significantly from 10.8±0.7 g/dL at baseline to 11.2±1.0 g/dL at Review 1 ($p< 0.05$). However, there was no significant change between Review 1 and Review 2 (mean± SD of 11.2±1.0 g/dL and 10.9±1.0 g/dL, respectively, $p > 0.05$). Notably, a significant increase was observed from Review 2 to Review 3, with levels rising from 10.9±1.0 g/dL to 11.1±0.9 g/dL ($p< 0.05$). Group B showed a significant increase in hemoglobin levels from 10.7±0.8 g/dL at baseline to 11.6±0.7 g/dL at Review 1 ($p> 0.05$). A significant decrease was observed between Review 1 and Review 2, with levels dropping from 11.6±0.7 g/dL to 10.9±1.0 g/dL ($p< 0.05$). However, hemoglobin levels increased significantly from Review 2 to Review 3, rising from 10.9±1.0 g/dL to 11.3±0.8 g/dL ($p< 0.05$). Group C experienced a significant increase in hemoglobin levels from 9.7±1.0 g/dL at baseline to 10.6±1.0 g/dL at Review 1 ($p< 0.05$). Hemoglobin levels remained stable between Review 1 and Review 2, at 10.6±1.0 g/dL for both time points ($p< 0.05$). Additionally, there was no significant change from Review 2 to Review 3, with levels consistently at 10.6±1.0 g/dL ($p< 0.05$).

Table 3: Hemoglobin levels and comparisons across groups

Group	Comparison	Mean±SD	Mean±SD	p-Value
Group A	Before & Review 1	10.8±0.7	11.2±1	<0.05
	Review 1 & 2	11.2±1	10.9±1	>0.05
	Review 2 & 3	10.9±1	11.1±0.9	<0.05
Group B	Before & Review 1	10.7±0.8	11.6±0.7	>0.05
	Review 1 & 2	11.6±0.7	10.9±1	<0.05
	Review 2 & 3	10.9±1	11.3±0.8	<0.05
Group C	Before & Review 1	9.7±1	10.6±1	<0.05
	Review 1 & 2	10.6±1	10.6±1	<0.05
	Review 2 & 3	10.6±1	10.6±1	<0.05

Table 4 summarizes the mean hemoglobin levels observed in three groups over a 3-month period, comparing baseline measurements with those recorded at the final review. Group A (Ferrous Fumarate) showed a baseline mean hemoglobin level of 10.8±0.7 g/dL, which increased to 11.1±0.9 g/dL by the final review. The p-value for the change from baseline to the final review was greater than 0.05, indicating that the overall increase in hemoglobin levels was not statistically significant. Group B (Ferrous Ascorbate) had a baseline mean hemoglobin of 10.7±0.8 g/dL, which rose significantly to 11.3±0.8 g/dL by the final review. The p-value for this change was less than 0.05, reflecting a statistically significant improvement in hemoglobin levels over the study period. Group C (Ferrous Pyrophosphate) started with a baseline mean hemoglobin of 9.7±1.5 g/dL and showed a notable increase to 10.6±1.4 g/dL by the final review. The p-value for this change was less than 0.05, indicating a significant increase in hemoglobin levels.

Overall, while Group A did not exhibit a significant overall change in hemoglobin levels, Groups B and C both demonstrated significant improvements by the end of the study.

Table 4: Hemoglobin mean values in three groups over a 3-month review period

Group	Before	Review 1 (1 Month)	Review 2 (2 Months)	Review 3 (3 Months)	p-Value (Before to Review 3)
A	10.8±0.7	11.2±1.0	10.9±1.0	11.1±0.9	>0.05
B	10.7±0.8	11.6±0.7	10.9±1.1	11.3±0.8	<0.05
C	9.7±1.5	10.6±1.5	10.6±1.5	10.6±1.4	<0.05

Table 5 summarizes the symptoms reported by patients in each group receiving different iron supplements. In Group A, the predominant symptoms were dizziness, reported by 4 patients, and nausea and vomiting, experienced by 3 patients. There was a single case of abdominal pain, and no patients reported tiredness, fatigue, or shortness of breath. Group B exhibited symptoms including dizziness in 2 patients, nausea and vomiting in 2 patients, and tiredness in 2 patients. Additionally, 2 patients in this group reported fatigue. Shortness of breath was noted but in only a few cases. In contrast, Group C had a significantly higher incidence of tiredness, with 7 patients affected. This group also reported 2 cases of shortness of breath, while no cases of abdominal pain or nausea and vomiting were observed. Fatigue was reported by 2 patients.

Overall, the symptom profiles varied across the groups, with Group C notably experiencing more cases of tiredness compared to Groups A and B.

Table 5: Symptoms experienced by patients in each group

Symptoms	Group A	Group B	Group C
Abdominal pain	1	0	0
Dizziness	4	2	1
Nausea and Vomiting	3	2	0
Tiredness	0	2	7
Fatigue	0	2	0
Shortness of breath	0	0	2
Total number of patients	8	8	10

Discussion

This study evaluated the efficacy and tolerability of three iron supplements Ferrous Fumarate, Ferrous Ascorbate, and Ferrous Pyrophosphate across 99 patients. Each group, consisting of 33 patients, received one of the supplements over a three-month period. The results revealed significant differences in both effectiveness and side effect profiles among the groups.

Group A, treated with Ferrous Fumarate, showed a notable initial increase in hemoglobin from 10.8±0.7 g/dL at baseline to 11.2±1.0 g/dL at the 1-month review. However, this improvement did not persist, as hemoglobin levels plateaued and then slightly declined, leading to a non-significant overall change by the final review ($p > 0.05$). These findings suggest that while Ferrous Fumarate can provide short-term benefits, its efficacy may diminish over extended periods, consistent with observations by Higgins *et al.* [4] regarding the variable long-term effectiveness of this supplement.

In contrast, Group B, which received Ferrous Ascorbate, demonstrated a significant and sustained improvement in hemoglobin levels. Starting from a baseline of 10.7±0.8 g/dL, hemoglobin levels increased significantly to 11.3±0.8 g/dL by the final review ($p < 0.05$). This sustained efficacy aligns with studies by Jafari *et al* [5], who reported Ferrous Ascorbate's superior ability to maintain elevated hemoglobin levels over time. Group B also experienced a moderate incidence of dizziness, nausea, and tiredness, which aligns with known side effects of Ferrous Ascorbate as detailed by Smith *et al.* [6].

Group C, receiving Ferrous Pyrophosphate, also achieved a significant increase in hemoglobin, from 9.7±1.5 g/dL at baseline to 10.6±1.4 g/dL by the final review ($p < 0.05$). Although hemoglobin levels stabilized after an initial increase, the overall improvement was substantial. The higher mean age in Group C may partially explain the differential response compared to the other groups, as older

adults often require different management strategies for anemia similar to Madhavan *et al*. [7]. This group reported a higher incidence of tiredness and shortness of breath, which reflects the distinct side effect profile of Ferrous Pyrophosphate.

The symptom profile varied significantly among the groups. Group A had the highest incidence of dizziness and nausea, with no reports of tiredness or shortness of breath. Group B had moderate reports of dizziness, nausea, and fatigue, suggesting a tolerability profile that is relatively consistent with prior studies by Smith *et al*., [6]. Notably, Group C reported a high incidence of tiredness and some shortness of breath, which could indicate a different side effect profile or response to Ferrous Pyrophosphate's absorption characteristics similar to Clark *et al* [8].

In summary, while Group B and Group C demonstrated significant improvements in hemoglobin levels by the end of the study, Group A did not show a statistically significant overall change. These results highlight the need to balance efficacy with patient tolerability when choosing an iron supplement for anemia management. Future research should further explore the long-term effects and side effect profiles of these supplements to better guide clinical decision-making.

Limitations

- The study was limited by a smaller sample size than initially planned. This may impact the generalizability of the findings. Larger studies are needed to confirm these results and provide more robust conclusions.
- The follow-up period of three months, while sufficient to observe short-term effects, may not capture long-term outcomes or the potential for delayed adverse effects. Extended follow-up would provide a clearer understanding of the long-term implications of using these iron supplements.
- Monitoring adherence and patient compliance more closely might reveal additional insights into the real-world effectiveness of these supplements.
- Conducting the study at a single center may limit the applicability of the findings to other settings. Multi-center trials could enhance the external validity of the results.

Conclusion

This study compared the efficacy and tolerability of Ferrous Fumarate, Ferrous Ascorbate, and Ferrous Pyrophosphate in treating iron deficiency anemia (IDA). Ferrous Ascorbate demonstrated the most consistent and significant improvement in hemoglobin levels, indicating its effectiveness for long-term management. In contrast, Ferrous Pyrophosphate also improved hemoglobin levels but was associated with a higher incidence of tiredness and shortness of breath. Ferrous Fumarate provided initial benefits but failed to sustain significant improvements over time. These findings underscore the need to balance efficacy and patient tolerability when selecting iron supplements to optimize treatment outcomes in IDA. Future research should focus on several key areas to enhance our understanding and management of IDA. Long-term studies are needed to evaluate the sustainability of hemoglobin improvements and detect any delayed side effects. Expanding the sample size and conducting multi-center trials could provide more robust data and enhance the generalizability of the results. Investigating the effects of these supplements across diverse populations, including different age groups and individuals with co-existing conditions, may offer more tailored treatment recommendations. Additionally, improving adherence tracking and patient compliance monitoring could provide further insights into the real-world effectiveness of these supplements. Exploring newer iron supplement formulations and delivery methods, along with conducting cost-effectiveness analyses, will be crucial for refining treatment strategies and making informed decisions, especially in resource-limited settings.

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