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Clinicians' Preferences and Perceptions of Iron Supplementation in the Treatment of Anemia in Indian Settings: Emphasis on Liposomal Iron Formulations

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Authors' contributions

This work was carried out in collaboration between both authors. Both the authors contributed equally in managing literature search, designing the study, performed the statistical analysis, wrote the protocol, and the first draft of the manuscript. Both of them read and approved the final manuscript.

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ABSTRACT

Background: Iron deficiency anemia remains a major public health issue in India, necessitating effective supplementation strategies. Recent advancements, such as liposomal iron formulations, have garnered attention for their enhanced bioavailability and tolerability. This study aimed to assess clinicians' preferences and experiences with iron supplementation, focusing on liposomal iron in the Indian clinical setting.

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Methodology: A cross-sectional study was conducted among clinicians across India from June 2023 to December 2023 using a multiple-response questionnaire. Clinicians were asked to complete the questionnaire independently, and responses were analyzed using descriptive statistics, with results presented as percentages. Data visualization, including pie and bar charts, was performed using Microsoft Excel 2013.

Results: The survey included 172 clinical experts and most clinicians (70%) preferred tablets for iron supplementation. A significant number (80%) of experts prescribed oral liposomal iron as their preferred formulation, citing its high bioavailability, ability to bypass restrictive intestinal barriers, and significantly higher plasma iron concentrations. Liposomal iron tablets were the most commonly used iron supplement among 79% of clinicians, reflecting advancements in formulations. Additionally, 39% of clinicians preferred oral liposomal iron in 26-50% of patients who experienced gastrointestinal side effects from other iron preparations, while 29% reported using it in less than 25% of such patients. A significant increase in hemoglobin levels with liposomal iron supplementation was noted by 61% of clinicians for both dialysis and non-dialysis patients. Furthermore, 51% found liposomal iron more tolerable than conventional preparations, with 57% rating its tolerability as excellent in their practice.

Conclusion: The study revealed a clear preference among clinicians for oral liposomal iron supplementation due to its high bioavailability, improved tolerability, and effectiveness in raising hemoglobin levels, particularly in patients who experienced gastrointestinal side effects with other iron formulations. These findings suggest that liposomal iron is becoming a favored option in clinical practice for treating anemia in Indian settings.

Keywords: Anemia; hemoglobin; liposomal iron; chronic kidney disease; conventional iron.

1. INTRODUCTION

Anemia is a widespread public health issue, impacting approximately one-third of the global population across both developing and developed nations [1]. It primarily affects young children, pregnant and postpartum women, as well as menstruating adolescent girls and women. The burden is highest in low- and lower-middle-income countries, particularly among populations in rural areas, impoverished households, and those with no formal education. Globally, an estimated 40% of children aged 6–59 months, 37% of pregnant women, and 30% of women aged 15–49 years were affected by anemia [2]. In 2021, the global prevalence of anemia across all age groups was 24.3% (95% uncertainty interval [UI] 23.9–24.7), representing 1.92 billion (1.89–1.95 billion) cases. Anemia accounted for 52 million (35.1–75.1) years lived with disability (YLDs) in 2021, and the YLD rate due to anemia decreased as the Socio-demographic Index improved [3]. In India, the National Family Health Survey (NFHS) 5, conducted between 2019 and 2021, found that the prevalence of anemia is 25% among men and 57% among women (aged 15-49 years) [4].

Anemia is a prevalent complication in chronic kidney disease (CKD) and is linked to diminished quality of life, poorer renal survival, increased morbidity and mortality, and elevated healthcare costs. Various studies examining the prevalence of anemia in non-dialysis-dependent CKD patients report rates as high as 60% [5]. According to an analysis by the National Health and Nutrition Examination Survey (NHANES), the prevalence of anemia rises with the progression of CKD, impacting 15.4% of CKD patients (approximately 4.8 million individuals). The prevalence of anemia was recorded at 17.4%, 50.3%, and 53.4% in CKD stages 3, 4, and 5, respectively [6]. Several studies conducted in India have reported a high prevalence of anemia among CKD patients [7-9].

The use of conventional iron preparations is linked to a range of side effects, including nausea, vomiting, flatulence, abdominal pain, diarrhea, constipation, dyspepsia, and the presence of black or tarry stools. These adverse effects are a primary concern associated with oral iron therapy. As many as 70% of patients taking oral iron preparations, particularly ferrous sulfate, report experiencing gastrointestinal (GI) side effects [10]. Liposomal iron represents a significant advancement in the treatment of iron deficiency anemia (IDA) that is unresponsive to conventional oral iron supplements. Liposomes are effective drug delivery systems, enabling targeted delivery of therapeutic agents while offering biocompatibility, biodegradability, and low toxicity. This next-generation oral iron preparation consists of ferric pyrophosphate

encapsulated in a phospholipid and lecithin membrane, resulting in high GI absorption and bioavailability with fewer side effects. Innovative technology uses liposomes to allow iron to be absorbed directly into the intestine without contacting the GI mucosa [11].

Though there are several advancements and clinical studies, there is a dearth of studies among physicians in actual practice. So, the present survey was intended to gather clinicians' perspectives and current trends in iron supplementation practices, with a specific focus on liposomal iron formulations. By examining clinicians' preferences, the study seeks to shed light on the factors driving the increasing use of liposomal iron and its perceived advantages in managing IDA, especially in patients who are intolerant to or inadequately responsive to traditional iron therapies.

2. MATERIALS AND METHODS

We carried out a cross-sectional, multiple-response questionnaire-based study involving clinicians with expertise in managing anemia due to chronic disease in the major Indian cities from June 2023 to December 2023. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

2.1 Questionnaire

The questionnaire booklet named FACT (Ferric Pyrophosphate Liposomal Formulation in Anemia due to CKD: Indian Expert Perspective Study) study was sent to the clinicians who were interested in participating in this study. The FACT study questionnaire included 18 items designed to gather feedback, clinical observations, and specialist experiences related to anemia and liposomal iron therapy.

2.2 Participants

An invitation was sent to leading clinicians in treating anemia in March 2023 for participation in this Indian survey. About 172 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. Participants were asked to complete the questionnaire without discussing it with their peers. A written informed consent was obtained from each physician before initiation of the study.

2.3 Statistical Methods

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, pie, and bar charts were created using Microsoft Excel 2013 (version 2409, build 16.0.18025.20030).

3. RESULTS

The survey included 172 clinicians, with the majority (55.81%) reporting the diagnosis of 11–25 cases of iron deficiency anemia per month in their clinical practice. Half of the clinicians (50%) indicated that 6–15% of their patients with iron deficiency anemia have hemoglobin levels below 8 g/dL. Approximately 68% of experts identified chronic kidney disease (CKD) as the most common chronic condition associated with anemia. According to 62% of respondents, 21–30% of their CKD patients suffer from iron deficiency anemia. Additionally, 53.49% of clinicians reported that 26–50% of their non-dialysis CKD patients are affected by iron deficiency anemia. The majority (55%) noted that fewer than 10% of their anemia patients require blood transfusions. When it came to educating CKD patients with anemia, most clinicians (37.79%) preferred one-on-one sessions. A significant portion (27.91%) favored small-group interactive sessions, while 26.74% preferred mass education through platforms such as social media or TV.

Approximately 40% of clinicians identified infusion reactions as the most common limitation associated with intravenous iron preparations, followed by poor compliance (33.72%) and iron overload with tissue damage (23.26%). Most clinicians (68%) reported that GI disturbances were the most common complaint among patients using conventional iron preparations. Additionally, 70% of clinicians preferred tablets as their method of iron supplementation in clinical practice (Table 1). Furthermore, 70% of clinicians favored ferric carboxymaltose as the intravenous iron formulation in their practice. A significant number of respondents (80%) prescribed oral liposomal iron as their preferred oral iron formulation (Fig. 1). Nearly 59% of clinicians identified increased bioavailability as a significant characteristic of liposomal iron (Table 2).

Table 1. Distribution of responses to the preferred method of iron supplementation in clinical practice

Iron supplementation method	Response rate (n = 172)
IV iron	49 (28.49%)
Tablets	121 (70.35%)
Syrups	1 (0.58%)
All of the above	1 (0.58%)

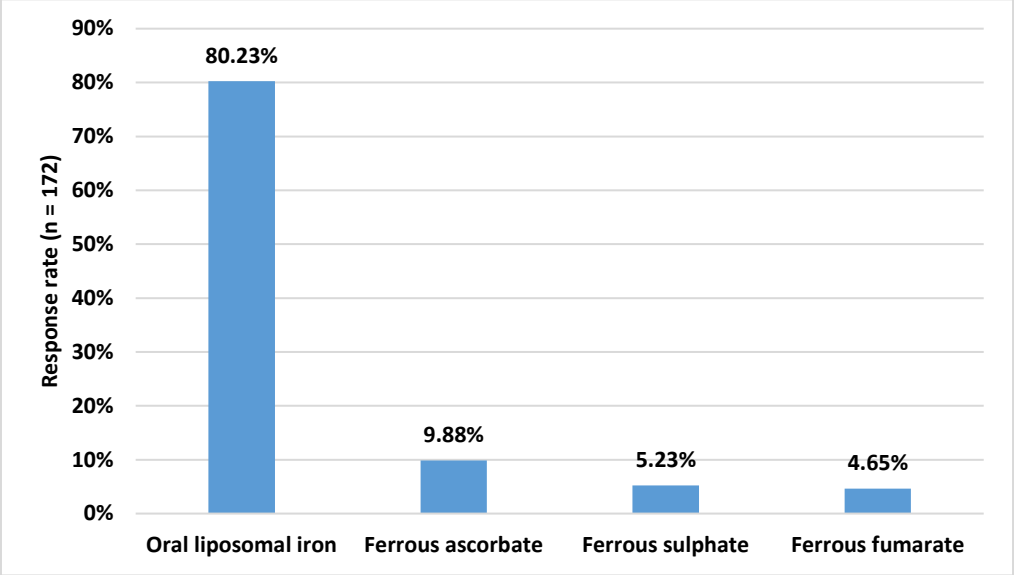

Fig. 1. Distribution of response to most prescribed oral iron formulations in clinical practice

Table 2. Distribution of responses to clinicians' perception of liposomal iron characteristics

Characteristics	Response rate (n = 172)
Highly bioavailable	102 (59.3%)
Bypasses the extremely restrictive	5 (2.91%)
Normal intestinal barriers	3 (1.74%)
Achieves much higher plasma iron concentration	22 (12.79%)
All of the above	40 (23.26%)

The majority of clinicians (79%) reported that liposomal iron tablets were the most commonly used iron supplement in their practice, reflecting advancements in formulations (Fig. 2). Approximately 39% preferred using oral liposomal iron in 26-50% of their patients who experienced GI side effects from other iron preparations, whereas 29% reported using it in less than 25% of such patients (Table 3). Most clinicians (61%) reported a significant increase in hemoglobin levels with liposomal iron in both dialysis and non-dialysis patients (Fig. 3).

Table 3. Distribution of response to frequency of using oral liposomal iron in patients with GI side effects from other iron preparations

Percentage of Patients	Response rate (n = 172)
<25% patients	50 (29.07%)
26-50% patients	68 (39.53%)
51-75% patients	35 (20.35%)
75-100% patients	19 (11.05%)

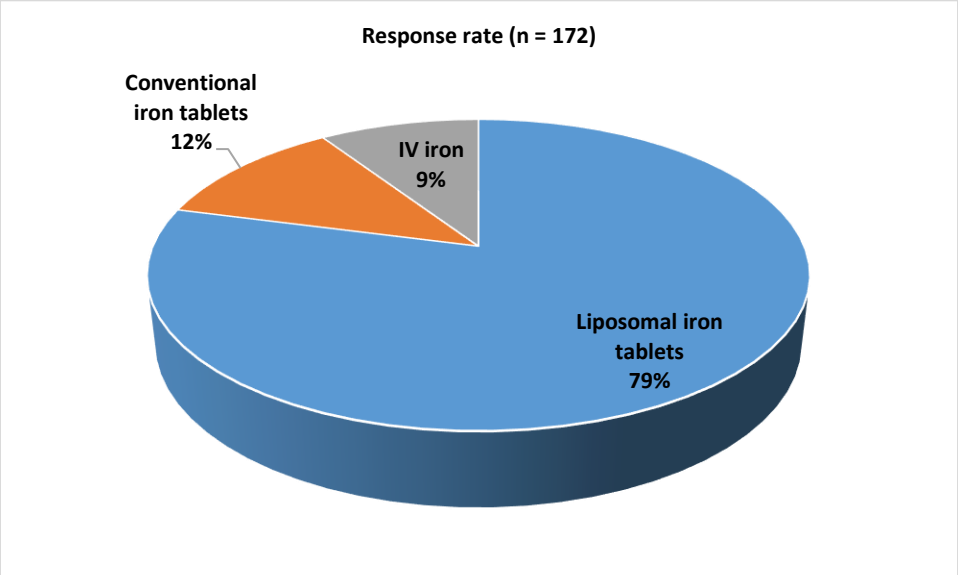

Fig. 2. Distribution of response to commonly used iron supplements with advances in formulations

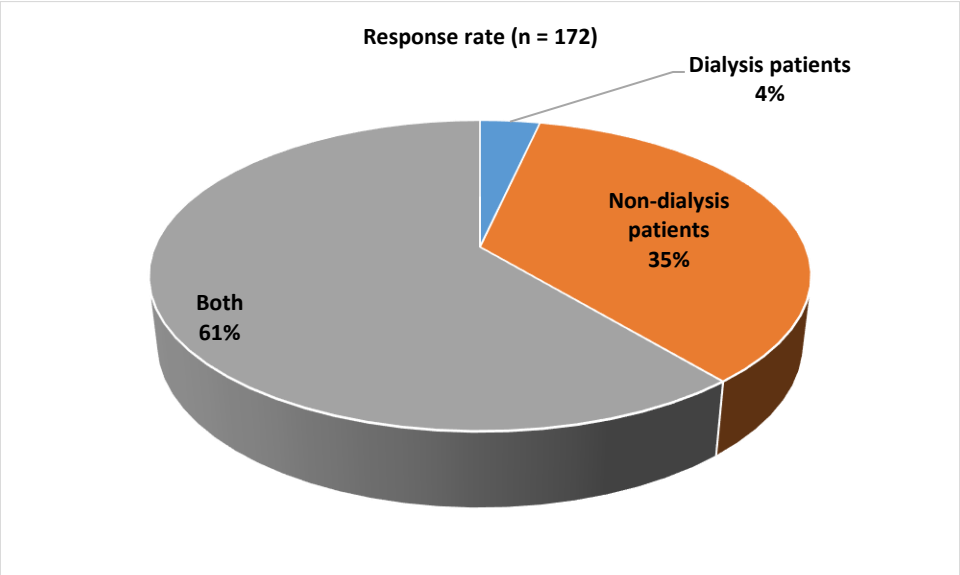

Fig. 3. Distribution of response to hemoglobin rise with liposomal iron in different patient groups

The majority of clinicians (51%) stated that liposomal iron offers better tolerance compared to conventional iron preparations (Table 4). More than half of clinicians (57%) rated the tolerability of liposomal iron as excellent in their clinical practice (Fig. 4).

Table 4. Distribution of response to clinicians' assessment of liposomal iron usage in patients

Response	Response rate (n = 172)
Effective in rising hemoglobin	52 (30.23%)
Better tolerance compared to conventional iron	88 (51.16%)
Better compliance	30 (17.44%)
All of the above	2 (1.16%)

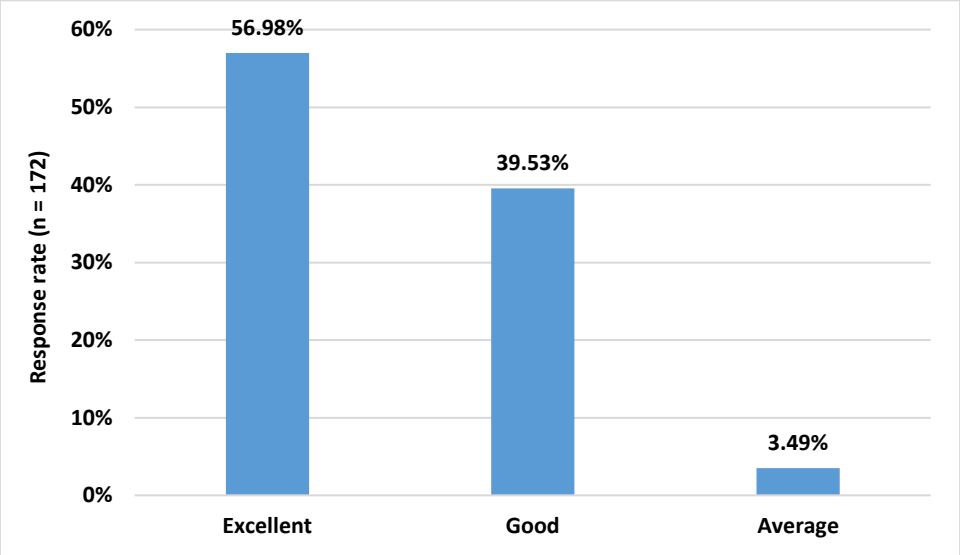

Fig. 4. Distributions of response to clinicians' rating of liposomal iron tolerability in clinical practice

4. DISCUSSION

The findings of the study revealed a strong preference for oral iron supplementation, specifically liposomal iron, among healthcare providers. The majority of the clinicians reported a preference for tablet forms of iron supplementation in their clinical practice. This preference aligns with the general trend in medicine towards non-invasive treatment options that offer patients convenience and ease of administration. Oral iron is typically the first-line therapy due to its convenience, widespread availability over the counter, and the low cost of its commonly used formulations [12].

Most respondents in the survey favored oral liposomal iron as their preferred formulation. This preference could be attributed to its unique properties such as higher bioavailability, the ability to bypass restrictive intestinal barriers, and superior plasma iron concentrations. These characteristics make liposomal iron particularly advantageous in clinical scenarios where traditional iron salts may be less effective or poorly tolerated. Additionally, the tolerability of liposomal iron, especially in patients experiencing gastrointestinal side effects from other iron preparations, was a key factor in its widespread use. The majority of clinicians reported using oral liposomal iron in 26-50% of their patients with GI side effects, affirming that it offers better tolerance than conventional iron preparations and rating its tolerability as excellent.

The absorption of conventional non-heme iron can be hindered by factors such as dietary inhibitors. Phytic acid, commonly found in cereal- and legume-based diets has been shown to significantly reduce iron absorption in both in-vivo studies and cell culture models. However, liposomal iron formulations, through advanced technological processing and a distinct absorption mechanism, provide improved iron delivery that is less impacted by these dietary inhibitors [12]. A review by Bhalla et al. found that the absorption and bioavailability of liposomal pyrophosphate iron was significantly higher compared to other iron formulations. Specifically, it was 3.5 times greater than free pyrophosphate iron, 2.7 times higher than iron sulfate, and 4.1 times higher than iron gluconate. The high bioavailability of liposomal iron, coupled with its reduced side effects and improved patient compliance, makes it an ideal option for individuals who require iron supplementation but are intolerant to oral treatments, unable to tolerate intravenous iron, or have poor iron absorption [13].

Pleşea-Condratovici et al. evaluated 30 post-menopausal women with iron deficiency anemia who had previously been treated with other iron supplements but experienced side effects. These women were administered liposomal iron supplements (microencapsulated iron pyrophosphate in liposomal form). After 8 weeks of supplementation, there was a significant increase in both hemoglobin and hematocrit levels. The therapy was well tolerated and did

not result in stomach upset and constipation commonly associated with other iron supplements [14]. Liposomal iron proved to be more effective than iron sulfate in increasing hemoglobin levels and reducing inflammatory markers in the treatment of anemia associated with chronic inflammatory diseases [15]. In a study by Montagud-Marrahi et al., patients with stable stage 3 CKD who experienced gastrointestinal intolerance to conventional oral iron therapy were treated with liposomal iron. After 6 months, there was a notable increase in hemoglobin levels compared to baseline, which was sustained at 12 months. The treatment was associated with a low rate of adverse reactions and demonstrated excellent tolerability [16].

In the current survey, a significant number of clinicians reported a significant increase in hemoglobin levels with liposomal iron in both dialysis and non-dialysis patients. A randomized trial by Pisani et al. involving 99 patients with stage 3-5 CKD who were not on dialysis and had iron deficiency anemia demonstrated that oral liposomal iron is a safe and effective alternative to intravenous iron gluconate for correcting anemia in non-dialysis CKD patients [17]. Pacara et al. found that in pediatric patients with CKD undergoing hemodialysis, liposomal iron treatment is comparable to intravenous iron in both safety and efficacy [18]. A study by Visciano et al. evaluated 21 patients with CKD stages 3, 4, and 5 with 14 receiving oral liposomal iron and 7 treated with intravenous iron. After 8 weeks, both groups showed an increase in hemoglobin levels compared to baseline. However, the increase was statistically significant only in the group receiving liposomal iron [19].

The key strength of the study is the use of a carefully designed and validated questionnaire to gather expert data. While this study provides valuable insights into clinicians' perceptions and practices regarding liposomal iron in treating anemia, it has some limitations. The survey-based data collection may be subject to recall bias or personal preferences that may not always align with evidence-based practice. Additionally, the study does not provide direct comparative data on patient outcomes between liposomal iron and other formulations. Clinical trials with larger cohorts and extended follow-up periods are necessary to determine the sustained benefits of liposomal iron in various patient populations, including those with different stages of CKD, anemia in chronic inflammatory diseases, and patients with GI intolerance to traditional iron supplements.

5. CONCLUSION

This study highlights a growing preference among clinicians for oral liposomal iron supplementation, primarily due to its perceived advantages in bioavailability, tolerability, and efficacy. Oral liposomal iron presents a promising alternative to intravenous iron, reducing the risk of infusion reactions and the need for hospital-based treatments.

CONSENT

As per international standards or university standards, participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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