

## Original Research Article

# Expert opinion on the clinical use and benefits of liposomal iron in the treatment of anemia in Indian settings

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## ABSTRACT

**Background:** Several studies have reported the effectiveness and safety of liposomal iron in increasing hemoglobin levels and correcting anemia. However, there was a dearth of information regarding the prescription pattern of physicians regarding its use and advantages in the actual practice. The present survey-based study aims at gathering clinicians' perspectives regarding the clinical use and benefits of liposomal iron in the treatment of anemia in Indian settings.

**Methods:** This cross-sectional study used a 19-item questionnaire to gather insights from specialists across different Indian settings regarding their perspectives on anemia and liposomal iron.

**Results:** Out of 124 participants, 77% opined that liposomal iron was highly bioavailable, achieves much higher plasma iron concentration, and bypasses the extremely restrictive, normal intestinal barriers. Oral liposomal iron was preferred by 77% of clinicians for the rapid increase in hemoglobin level and 99% of clinicians reported improved patient compliance with liposomal iron therapy for anemia. According to 50% of clinicians, oral liposomal iron was effective in non-hemodialysis dependent chronic kidney diseases and 87% of clinicians reported that patients without CKD needed oral liposomal iron. Half of the respondents reported a significant increase in Hb with liposomal iron in both dialysis and non-dialysis patients.

**Conclusions:** The survey participants reported that liposomal iron treatment for anemia was beneficial in treating both CKD and non-CKD patients. The survey findings have corroborated the advantages of liposomal iron for treating anemia such as increased bioavailability, rapid and effective increase in Hb level, better patient compliance and tolerability, decreased side effects, cost-effectiveness, and flexible dosing.

**Keywords:** Anemia, Hemoglobin, Liposomal iron, Chronic kidney disease, Conventional iron

## INTRODUCTION

The 2021 Global Burden of Disease Study reported the prevalence of anemia across all ages as 24.3%, corresponding to 1.92 billion prevalent cases. Anemia caused 52 million years lived with disability (YLDs) in 2021.<sup>1</sup> Approximately 40% of all children aged 6-59 months, 37% of pregnant women, and 30% of women aged 15-49 years were affected by this condition.<sup>2</sup> In

India, the National Family Health Survey (NFHS) 5 conducted in 2019-21 revealed that anemia prevalence was 25% in men (aged 15-49 years) and 57% in women (aged 15-49 years). For other groups, the prevalence was 31% in adolescent boys (aged 15-19 years), 59% in adolescent girls, 52% in pregnant women (aged 15-49 years), and 67% in children (aged 6-59 months).<sup>3</sup> According to the World Health Organization (WHO), iron deficiency accounts for 50% of all anemia cases.

Progress on anemia in women aged 15 to 49 years has not kept pace with the World Health Assembly (WHA) global nutrition aim to halve the incidence of anemia by 2030 on a global, regional, and practically universal scale. The prevalence of anemia in children has also remained high.<sup>4</sup> Progress in addressing anemia among females aged 15 to 49 years has not been aligned with the WHA global nutrition goal to reduce the anemia incidence worldwide, regionally, and universally by 2030.<sup>4</sup> Low iron intake, chronic blood loss of varying degrees, and malabsorption were the primary causes of iron deficiency anemia (IDA). Additionally, IDA was commonly related to several chronic illnesses, including inflammatory bowel disease (IBD), cancer, chronic heart failure, and chronic kidney disease (CKD). IDA was prevalent among many adult and elderly patients in internal medicine departments.<sup>5</sup>

Anemia is a common comorbidity of CKD, associated with significant burden due to decreased patient health-related quality of life, worse renal survival, increased morbidity and mortality, higher treatment costs, and increased healthcare resource utilization.<sup>6</sup> According to National health and nutrition examination survey (NHANES) analysis, anemia prevalence increases with the CKD stage, affecting 15.4% (approximately 4.8 million people) of CKD patients. Anemia prevalence was 17.4%, 50.3%, and 53.4% in stages 3, 4, and 5 CKD, respectively.<sup>7</sup> Several Indian studies also reported a high prevalence of anemia in CKD patients.<sup>8-10</sup> Several studies have reported the effectiveness and safety of liposomal iron in increasing hemoglobin (Hb) levels and correcting anemia,<sup>11-16</sup> whereas conventional oral iron treatment has several limitations due to dose-dependent adverse effects, low absorption, poor compliance, and limitations in a variety of inflammatory disorders. Unlike traditional oral iron preparations, liposomal iron represents a highly advanced, unique form of iron therapy that provides improved tolerance, higher absorption and bioavailability, and fewer gastrointestinal side effects due to the distinct delivery mechanism.<sup>17</sup> However, there was a dearth of information regarding the prescription pattern of physicians regarding its use and advantages in the real world scenario. The objective of the present survey-based study is to gather clinicians' perspectives regarding the clinical use and benefits of liposomal iron for the treatment of anemia in Indian settings.

## METHODS

We carried out a cross sectional, multiple-response questionnaire-based survey among clinicians specialized in treating anemia patients across major cities in India from June 2022 to December 2022. An invitation was sent to leading clinicians in managing anemia in the month of March 2022 for participation in this Indian survey. About 124 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Further, we excluded those who were not interested

to participate in this study. The questionnaire booklet titled FACT (Ferric pyrophosphate liposomal formulation in anemia due to chronic diseases: an Indian study) study was sent to the physicians and the questionnaire consisted of 19 items intended to gather current feedback, clinical observations, and clinical experience of specialists on anemia and liposomal iron therapy. Physicians were asked to complete the questionnaire without discussing with peers. A written informed consent was obtained from each clinician's prior initiation of the study.

## Statistical analysis

The data were analyzed by 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 16.0.13901.20400).

## RESULTS

The study involved 124 clinicians as study participants. According to 41% of the study subjects, 21-30% of patients were diagnosed with iron deficiency anemia due to chronic diseases in a month. Nearly 81% of the clinicians reported CKD as the common chronic illness causing anemia. According to 60% and 35% of respondents, adults, and geriatrics were more likely to have iron deficiency anemia. According to 46%, 31%, and 11% of respondents, infusion reactions, iron overload, tissue damage, and poor compliance were the disadvantages associated with IV iron preparations, respectively. Also, all the respondents reported that conventional iron preparations were associated with lower bioavailability, gastrointestinal side effects, and poor anemia compliance due to chronic diseases. About 77% of the respondents agreed on all three benefits of liposomal iron, namely increased bioavailability, attainment of higher plasma iron concentration, and bypassing the extremely restrictive normal intestinal barriers (Table 1). About 50% of the respondents reported a significant increase in Hb levels in both dialysis and non-dialysis patients. In stages 3, 2, and 1 of renal illness, 38%, 31%, and 24% of responders favored oral liposomal iron. Approximately 42% of the respondents reported 45-60 years to be the most common age group preferred to prescribe liposomal iron. According to 48% of the respondents, a 60 mg dose of liposomal iron was required to raise sufficient Hb in a week in stage 4 CKD patients. Half of the respondents reported more than 30 patients may require oral liposomal iron in their monthly clinical practice. According to the majority of clinicians (47%), oral liposomal iron enhances erythropoietin stimulating agents (ESAs) therapy by 30-50%. In clinical practice, nearly 77% of clinicians preferred oral liposomal iron for its rapid increase in Hb levels, and 99% reported better

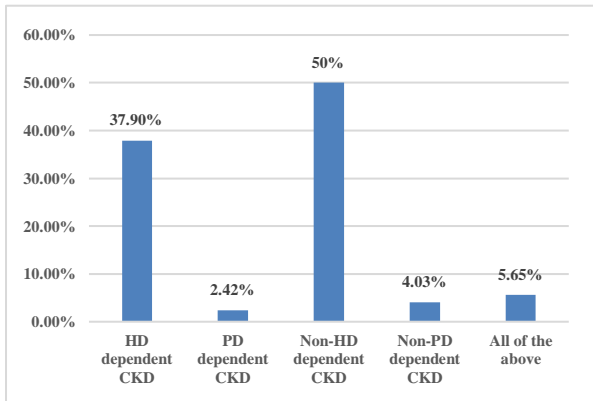
patient compliance with liposomal iron therapy for anemia (Table 2).

**Table 1: Distribution of response to pharmacological characteristics of liposomal iron (n=124).**

| Pharmacological characteristics                                | Response rate, N (%) |
|--|----------------------|
| High bioavailability   | 24 (19.35)           |
| Bypasses the extremely restrictive, normal intestinal barriers | 1 (0.81)             |
| Achieves much higher plasma iron concentration                 | 4 (3.23)             |
| All of the above   | 95 (76.61)           |

**Table 2: Distribution of response to preference of liposomal iron for the rapid increase in Hb level and better patient compliance in routine clinical practice (n=124).**

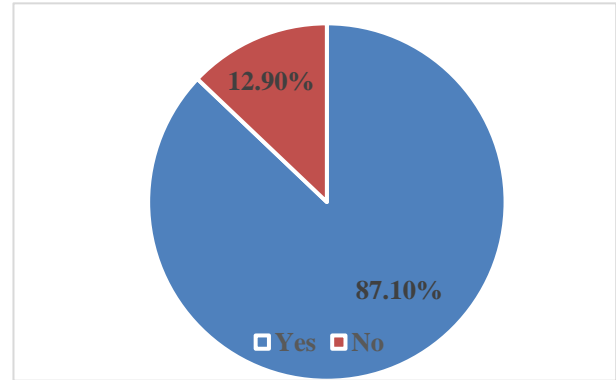
| Preference | Response rate, N (%)                               |  |
|------------|--|--|
|            | Oral liposomal iron for the rapid rise in Hb level | Patient compliance is better when treated with liposomal iron therapy for anemia |
| Yes        | 95 (76.61)   | 123 (99.19)  |
| No         | 29 (23.39)   | 1 (0.81)   |



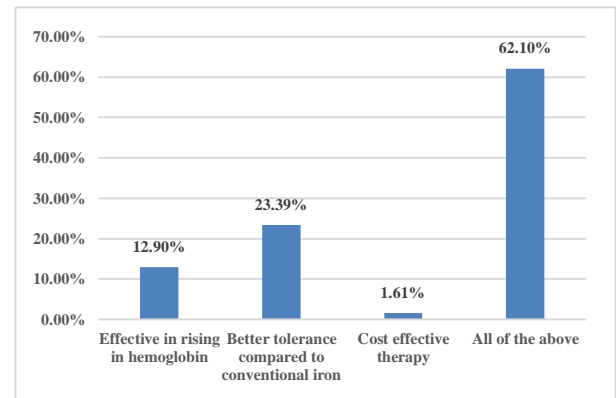
**Figure 1: Distribution of response to clinical effectiveness of oral liposomal iron in various CKD subgroups (HD: Hemodialysis; PD: Peritoneal dialysis).**

Half of the clinicians reported the effectiveness of oral liposomal iron in non-hemodialysis-dependent CKD, while 38% of respondents preferred it for hemodialysis-dependent CKD (Figure 1). The need for oral liposomal iron in non-CKD patients was noted by a substantial percentage of the clinicians (87%) (Figure 2). According to 52% and 42% of clinicians, the tolerability of liposomal iron was excellent and good respectively (Table 3). Over 62% of the clinicians agreed on all three benefits of liposomal iron compared to conventional iron

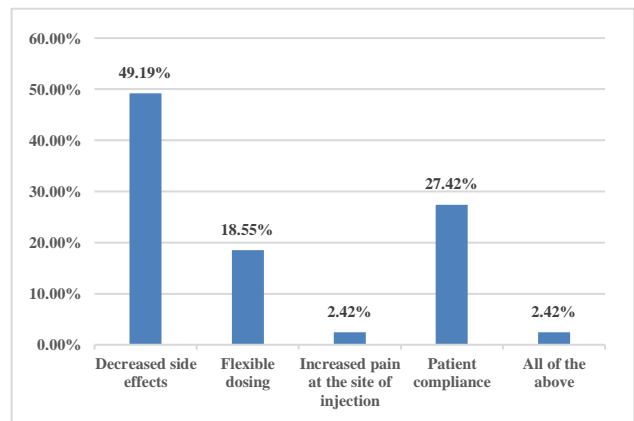
namely better tolerability, effectiveness in increasing Hb levels, and cost-effectiveness (Figure 3).



**Figure 2: Distribution of response to clinicians' preference on the requirement of oral liposomal iron in non-CKD patients.**



**Figure 3: Distribution of response to use of liposomal iron in anemic patients.**



**Figure 4: Distribution of response to advantages of using oral liposomal iron compared to conventional IV iron.**

According to 49%, 27%, and 18% of the clinicians, compared to conventional intravenous (IV) iron, oral liposomal iron has decreased side effects, better patient compliance, and flexible dose, respectively (Figure 4).

**Table 3: Distribution of response to rate of tolerability of liposomal iron (n=124).**

| Rate of tolerability | N (%)      |
|----------------------|------------|
| Excellent            | 64 (51.61) |
| Good                 | 52 (41.94) |
| Average              | 5 (4.03)   |
| Poor                 | 3 (2.42)   |

## DISCUSSION

The study emphasizes the significant preference of liposomal iron over traditional IV iron therapy for the treatment of anemia. The findings also underscore the advantages of liposomal iron in treating both CKD and non-CKD patients in terms of bioavailability, tolerability, and cost-effectiveness. In the present survey, majority of the clinicians preferred liposomal iron for anemic patients due to its ability to increase plasma iron concentration and bypass the extremely restrictive normal intestinal barriers. In a similar study, Antune et al reported a significant increase in the Hb level (mean increase of Hb from 11.4 to 12.6 g/dl) in approximately 62% of the participants with the use of oral liposomal iron treatment. The study also demonstrated an average increase in the transferrin saturation index by 10.2 ( $p=0.006$ ) and a 26.3-point improvement in the quality of life ( $p<0.0001$ ).<sup>18</sup> A review by Bhalla and Kaushal concluded that the distinguishing features of liposomal iron, such as high bioavailability, fewer side effects, and good compliance, make it suitable for use in patients who require iron administration and were intolerant to traditional oral or IV treatment, or have poor absorption.<sup>19</sup> According to the current survey participants, oral liposomal iron was more effective at increasing Hb levels in patients with non-hemodialysis-dependent CKD. In a comparative study, Pisani et al found that oral liposomal iron was a safe and effective alternative to IV iron gluconate for correcting anemia in non-dialysis CKD patients. Patients receiving oral liposomal iron exhibited significant improvements in Hb levels, ferritin levels, and transferrin saturation.<sup>12</sup>

The present study reported that liposomal iron can increase Hb levels in patients with or without dialysis-dependent CKD. Malhotra et al have also suggested that taking two capsules of liposomal iron daily could be an alternative therapy for hemodialysis patients with iron deficiency.<sup>5</sup> A prospective observational study by Montagud-Marrahi noted that treatment with liposomal iron resulted in a significant increase in Hb levels in CKD stage 3 patients, detectable at 6 months ( $0.49\pm 0.19$  g/dl increase compared to baseline) and maintained at 12 months ( $0.36\pm 0.19$  g/dl increase). The study has also reported its potential as a first-line treatment for anemia in CKD patients, particularly those who exhibit intolerance to conventional oral treatments due to its lower incidence of adverse reactions and excellent tolerability.<sup>14</sup> Liposomal iron was efficient in increasing the Hb in CKD patients as well as in patients with iron deficiency anemia. Visciano et al observed that the

increase in Hb levels at 8 weeks, compared to baseline, was similar in both the IV and liposomal groups, but it reached significance only in the liposomal group.<sup>20</sup> In a study conducted by Condratovici et al 30 post-menopausal females suffering from iron deficiency anemia (Hb  $<11.5$  g/dl) and who had previously experienced side effects with other iron supplements were provided with a liposomal iron supplement containing microencapsulated iron pyrophosphate. After eight weeks of supplementation, a significant increase in Hb and hematocrit levels was observed, and the treatment was well-tolerated. The study also showed statistically significant improvements in most of the side effects previously experienced by the patients.<sup>21</sup> Hussain et al also reported an increased mean serum Hb level in women of reproductive age, rising from 8.71 to 10.47 by the end of 12 weeks from the baseline ( $p<0.001$ ).<sup>11</sup>

Marrahi et al found a sustained increase in Hb levels from baseline up to 12 months. The study also revealed that liposomal iron had a low rate of adverse reactions and was well-tolerated as a first-line treatment for anemia in patients with CKD, particularly in those who were intolerant to conventional oral iron treatment.<sup>14</sup> Liposomal iron supplements can expedite the recovery of Hb levels. Additionally, they can reduce the costs associated with surgical procedures. Scardino et al showed that the use of liposomal iron supplements before surgery resulted in shorter hospital stays and fewer blood transfusions.<sup>22</sup> The survey results offer valuable insights into the effectiveness of liposomal iron in treating anemia. The major strength of the study was the use of a carefully designed and validated questionnaire to collect expert data. However, it was important to acknowledge the potential influence of personal perspectives and preferences, which may introduce bias. It was important to consider this limitation while generalizing the study findings.

## CONCLUSION

The study provides valuable insights into the usage and benefits of liposomal iron in Indian settings. The clinicians reported the effectiveness of liposomal iron therapy for anemia in both CKD and non-CKD patients. The expert survey has highlighted the higher bioavailability, the rapid and effective increase in Hb level, better patient compliance, better tolerability and decreased side effects, cost effectiveness, and flexible dosing of liposomal iron, suggesting it to be an effective therapy for treating anemia in clinical practice.

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