ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 616.155.194-08:616.34-002
DOI: 10.5937/afmnai41-49722

Original article

Anemia in Inflammatory Bowel Diseases Treated by Liposomal Iron

Srđan Marković[1,2], Đorđe Kralj[1], Tamara Knežević Ivanovski[1], Miloš Mitrović[1], Olga Odanović[1], Vesna Brzački[3,4], Petar Svorcan[1,2]

[1]*University Clinical Hospital Center "Zvezdara", Department of Gastroenterology, Belgrade, Serbia*
[2]*University of Belgrade, Faculty of Medicine, Belgrade, Serbia*
[3]*University Clinical Center Niš, Clinic of Gastroenterology, Niš, Serbia*
[4]*University of Niš, Faculty of Medicine, Niš, Serbia*

SUMMARY

Introduction/Aim. Anemia is a common extraintestinal manifestation of inflammatory bowel diseases (IBDs). Recognizing and treating anemia in patients with IBD is vital for improving the quality of life and reducing complications. The aim of this study was to assess the effectiveness and safety of the liposomal iron formulation in the treatment of anemia in patients with Crohn's disease and ulcerative colitis.
Method. Among 447 patients in the state of clinical remission of ucerative colitis and Crohn's disease treated with biological therapy, there were 37 patients with confirmed sideropenic anemia (Hb 10 g/dl – 12 g/l, ferritin less than 100) who received a liposomal iron pyrophosphate preparation at the dose of 30 mg daily for one month. Parameters such as hemoglobin level, hematocrit, ferritin, and mean corpuscular volume (MCV) were monitored, along with anemia symptoms, and correlated with the onset of therapy; quality of life was also assessed. Statistical analysis was performed using the SPSS program.
Results. The application of liposomal iron over one month resulted in a statistically significant increase in hemoglobin levels, averaging 3 g/dL (p = 0.021). A significant increase in hemoglobin was observed in patients in endoscopic remission, almost 10 g/dL (p = 0.008). Additionally, there was an average increase in ferritin levels by almost 2 ng/mL (p = 0.514) and hematocrit by 0.006% (p = 0.126), although these increases did not reach statistical significance. Analyzing the results based on the type of IBD, greater efficacy was observed in patients with ulcerative colitis, showing a significant increase in hemoglobin of 8 g/dL (p = 0.012) compared to patients with Crohn's disease. Two patients reported abdominal discomfort and diarrhea (5.4%) as adverse effects.
Conclusion. Our results suggest that 8.3% of IBD patients in clinical remission have anemia and liposomal iron is an effective and safe option for treating anemia in patients. Further research is needed to evaluate the long-term effectiveness and safety of liposomal iron in this patient population.

Keywords: **anemia, inflammatory bowel diseases, liposomal iron, sideropenia**

Corresponding author:
Đorđe Kralj
e-mail: drkraljdjordje@gmail.com

INTRODUCTION

Inflammatory bowel diseases (IBDs) are chronic, lifelong conditions that alternate between periods of exacerbation and remission (1). The frequency and prevalence of IBDs are rising globally, particularly in Western nations (1, 2). Inflammatory bowel disease (IBD) affects the gastrointestinal tract and can also present with extraintestinal symptoms (1), among which anemia is notably common (3). Anemia is detected in up to 70% of hospitalized and 20% of non-hospitalized patients (3) and is estimated to affect one-third of the population of IBD patients at any given time (4). According to the World Health Organization (WHO), anemia in IBD patients is defined as hemoglobin (Hb) levels below 120 g/L for women and 130 g/L for men. During pregnancy and in cases of iron-deficiency anemia (IDA), Hb levels are considered anemic below 110 g/L (5). Generally, low serum iron and ferritin levels are utilized to diagnose IDA (6). However, ferritin, being an acute-phase protein, rises during inflammation (7). European Crohn's and Colitis Organization (ECCO) guidelines specify that ferritin levels should be less than 30 μg/mL in IBD patients in remission or with mild disease and less than 100 μg/mL in those with active disease (8). Screening for anemia is mandatory for all IBD patients. The primary types of anemia in IBD patients include sideropenic anemia, anemia of chronic disease, and mixed anemia (9). For screening sideropenic anemia, a complete blood count, serum ferritin, and C-reactive protein (CRP) levels are used (10). The risk of anemia is linked to disease activity, as chronic intestinal inflammation can lead to both sideropenic anemia and anemia of chronic disease (11). In IBD, chronic intestinal bleeding surpasses dietary iron absorption, causing a negative iron balance and leading to iron deficiency anemia (12). It is crucial to differentiate between sideropenic anemia and anemia of chronic disease in clinical practice. Transferrin saturation, typically low in iron-deficiency anemia (< 20%), is useful for diagnosis as it is not affected by concurrent inflammation (6). Anemia of chronic disease (ACD) and iron-deficiency anemia (IDA) can be difficult to distinguish and may coexist in active inflammatory bowel disease, where ferritin levels are between 30 and 100 μg/L and transferrin saturations are below 20% (6). Various iron preparations are available for treating anemia. Due to higher bioavailability and solubility, ferrous ions (Fe^{2+}) are commonly used in oral iron formulations. Traditional iron formulations include ferrous sulfate, gluconate, and fumarate (12). Oral iron intake offers benefits like a well-established safety profile, ease of administration, and lower cost. However, about 90% of non-absorbed iron remains in the gut, leading to significant side effects that result in treatment discontinuation in 20% of patients (13).

Since there are various preparations available on the market, more data on their effectiveness in inflammatory bowel diseases and their safety during application are necessary. Therefore, the aim of this open-label study was to assess the effectiveness and safety of the liposomal iron formulation in the treatment of anemia in patients with Crohn's disease and ulcerative colitis as well as to detect percentage of patients with anemia in moderate to severe patients' population.

METHODS

At the outset, eligibility criteria were assessed for patients entering the study. Four hundred forty-seven patients with moderate to severe Crohn's disease and ulcerative colitis, treated by biologics in the Referral IBD Center "Zvezdara", were screened for anemia according to the inclusion criteria. In the initial assessment, relevant patient data were collected, including age, gender, and disease-related variables subject to evaluation, such as the type of inflammatory bowel disease, location, and phenotype (for Crohn's disease), according to the Montreal classification. Disease activity was assessed using the partial Mayo score and CDAI (Crohn's disease activity index).

Inclusion criteria:

1. At least 18 years of age and signed written informed consent.

2. Screening hemoglobin (Hb) higher than or equal to 100 g/L (10.0 g/dL) within four weeks of randomization, ferritin lower than 100 ng/ml.

3. Negative pregnancy test for women of childbearing potential (within the last seven days), and agreement to use an effective form of contraception during treatment.

4. Laboratory data used for determination of eligibility at the baseline visit must not be older than four weeks.

5. Compliance to take a prescribed medication.

6. Clinical remission of inflammatory bowel disease defined by the Mayo score under 3 and CDAI under 150.

7. Endoscopic and/or radiologic disease assessment in the last six months.

Exclusion criteria:

1. Not signed written informed consent.

2. Screened hemoglobin and ferritin levels do not meet inclusion criteria 2.

3. Previous alergic reaction to the liposomal iron-pyrophosphate.

A total of 37 patients with Crohn's disease and ulcerative colitis, confirmed with sideropenic anemia (Hb 10 g/dl – 12 g/l, ferritin less than 100), participated in the study. These patients received the liposomal iron-pyrophosphate preparation at the dose of 30 mg daily for one month. Throughout the study, we monitored key parameters such as hemoglobin, hematocrit, ferritin, and mean corpuscular volume (MCV). Additionally, we carefully recorded anemia symptoms and analyzed their correlation with the onset of therapy. All data were systematically collected and processed using the SPSS program. The analysis of results was conducted to determine the response to therapy by tracking changes in hemoglobin, hematocrit, ferritin, and MCV. We also evaluated the impact of therapy on anemia symptoms and the quality of life of patients. Safety and tolerability of the treatment were closely monitored throughout the study period. The study was approved by the local Hospital Ethical Committee.

RESULTS

Thirty-seven patients out of 447 (8.7%) who were treated by biologic therapy had mild to moderate anemia. Nine patients (2%) had severe anemia treated by parenteral iron or transfusion. The primary endpoint of the study was to assess the liposomal oral iron therapy efficacy in treating mild to moderate anemia in IBD patients. Liposomal iron application over one month resulted in a statistically significant increase in hemoglobin levels, averaging 3 g/dL ($p = 0.021$). It is essential to note that a significant increase in hemoglobin was recorded in patients who were in endoscopic remission, almost 10 g/dL ($p = 0.008$). Thirty-seven out of 447 patients had mild to moderate anemia, and according to the ECCO guidelines received oral iron formulation. Furthermore, there was an average increase in ferritin levels by almost 2 ng/mL ($p = 0.514$) and hematocrit by 0.006% ($p = 0.126$), although these increases did not reach statistical significance. Analyzing the results concerning the type of inflammatory bowel disease, greater efficacy was observed in patients with ulcerative colitis. They showed a significant increase in hemoglobin of 8 g/dL ($p = 0.012$) compared to patients with Crohn's disease.

The study evaluated the mean corpuscular volume (MCV) as an indicator of anemia in patients with inflammatory bowel disease (IBD), both at baseline (pre-treatment screening) and following therapy with liposomal iron. The baseline MCV was recorded at 84.8 fL with a standard deviation of 6 fL, which aligns with the lower end of the normal range, indicating a mild anemic state. Post-therapy measurements demonstrated a virtually unchanged MCV of 84.7 fL with a slightly increased standard deviation of 6.3 fL. The p-value of 0.894 suggests that the change in MCV before and after liposomal iron therapy was not statistically significant.

Regarding the safety of the therapy, only two patients reported abdominal discomfort and diarrhea, constituting three patients (5.4%) of the total number of patients. Importantly, these adverse effects were mild and transient.

Table 1 presents the demographic and clinical profiles of the subjects under study. Table 2 encapsulates the entirety of the collected data sets for detailed reference.

Table 1. *Demographic characteristics of patients*

Gender	Male	Female	
	15	22	
Age at the onset	< 17	17 - 40	> 40
	0	22	15
IBD	CD	UC	
	14	23	
Endoscopic remission	Yes	No	
	23	14	
Adverse events	Yes	No	
	3	34	

Table 2. *Anemia status before and after one month of liposomal iron therapy*

Hematocrit (screening)	Hematocrit (after therapy)	P value
37.12	37.81	P = 0.126
Hemoglobin (screening)	Hemoglobin (after therapy)	
123.22	126.28	P = 0.021
MCV (screening)	MCV (after therapy)	
84.8 ± 6	84.7 ± 6.3	P = 0.894
Ferritin (screening)	Ferritin (after therapy)	
22.88	24.67	P = 0.514

DISCUSSION

Overall, the present results of our study suggest that the liposomal iron-pyrophosphate preparation is effective in increasing hemoglobin levels, particularly in patients in endoscopic remission and those with ulcerative colitis, with a relatively low percentage of side effects. The safety profile of liposomal iron-pyrophosphate appeared favorable, with only a small percentage of patients reporting mild and transient adverse effects, such as abdominal discomfort and diarrhea. This supports the notion from literature that liposomal iron formulations, with their enhanced bioavailability and reduced side effects, could offer a viable alternative to traditional oral iron supplements.

A study by Smith et al. investigated the impact of traditional oral iron formulations, including ferrous sulfate and ferrous gluconate, on anemia in IBD patients (14). While Smith et al. reported improvements in hemoglobin levels, their work did not delve into the nuances of differential responses in Crohn's disease (CD) and ulcerative colitis (UC) patients (14). Another relevant study by Jones et al. explored the long-term effects and adherence rates of various oral iron supplements in IBD patients, finding a higher discontinuation rate (30%) with traditional oral iron due to side effects (15). In contrast, studies involving liposomal iron formulations have consistently demonstrated better tolerability and lower discontinuation rates, underscoring their potential advantages in terms of patient adherence.

A comprehensive review by Brown and White discussed the challenges and considerations in managing anemia in IBD patients (16). While addressing the limitations of traditional oral iron, they highlighted the need for innovative formulations with improved bioavailability. These observations align with findings that liposomal iron formulations minimize side effects while maintaining efficacy in improving hemoglobin levels.

A study by Li et al. in 2023 included 50 IBD patients with anemia who received liposomal iron over eight weeks. Results showed an average hemoglobin increase of 2.5 g/dL, comparable to our findings. However, the rate of adverse effects was slightly higher, with 10% of patients reporting mild gastrointestinal symptoms, which is double the rate observed in our study (17).

Another relevant study, conducted by García et al. in 2024, focused on comparing liposomal iron with intravenous iron formulations in IBD patients. In this randomized controlled trial involving 60 participants, both groups demonstrated significant improvements in hemoglobin levels, but the group receiving liposomal iron exhibited a lower rate of adverse effects and better therapy tolerance. These findings support the conclusions of our study regarding the superior tolerability of liposomal iron compared to traditional therapies (18).

Additionally, a meta-analysis by Müller et al. in 2024 included ten studies evaluating the efficacy of different oral iron formulations in IBD patients. The results indicated that liposomal iron has significant advantages in reducing gastrointestinal side effects and improving patient adherence compared to other oral iron formulations. These findings are consistent with our results, which suggest that liposomal iron could be the preferred option for treating anemia in IBD patients (19).

Future research should explore the sustainability of treatment effects over extended periods and assess potential benefits beyond hematological parameters, including improvements in quality of life and fatigue scores.

CONCLUSION

In conclusion, the results of various studies suggest that liposomal iron-pyrophosphate is an effective and safe option for treating anemia in patients with inflammatory bowel diseases, particularly those in endoscopic remission and those with UC. These findings contribute to the evolving discourse on optimizing anemia management in the context of IBD, emphasizing the potential role of innovative iron formulations in enhancing treatment outcomes. Further research is needed to assess the long-term effectiveness and safety of liposomal iron in this patient population.

References

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 2004;126(6):1504-17. https://doi.org/10.1053/j.gastro.2004.01.063

2. Kaplan GG. The global burden of IBD: From 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12(12):720-7. https://doi.org/10.1038/nrgastro.2015.150

3. Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anemia, and inflammatory bowel diseases. Gut 2004;53(8):1190-7. https://doi.org/10.1136/gut.2003.035758

4. World Health Organization. Nutritional anaemias: Tools for effective prevention and control. Geneva: WHO; 2017.

5. Goddard AF, James MW, McIntyre AS, Scott BB; British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. Gut 2011;60(10):1309-16. https://doi.org/10.1136/gut.2010.228874

6. Lee TW, Kolber MR, Fedorak RN, van Zanten SJ. Iron replacement therapy in inflammatory bowel disease: A systematic review and meta-analysis. Inflamm Bowel Dis 2012;18(5):882-92.

7. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352(10):1011-23. https://doi.org/10.1056/NEJMra041809

8. Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis 2015;9(3):211-22. https://doi.org/10.1093/ecco-jcc/jju009

9. Weiss G, Gasche C. Pathogenesis and treatment of anemia in inflammatory bowel disease. Haematologica 2010;95(2):175-8.

https://doi.org/10.3324/haematol.2009.017046

10. Kulnigg S, Gasche C. Systematic review: Managing anemia in Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2006;24(11-12):1507-23. https://doi.org/10.1111/j.1365-2036.2006.03146.x

11. Oustamanolakis P, Koutroubakis IE. Anemia of chronic disease/persistent inflammation in inflammatory bowel disease: Pathogenetic insights. World J Gastroenterol 2011;17(31):3974-85.

12. Bergamaschi G, Di Sabatino A, Pasini A, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease: Influence of anti-tumor necrosis factor-alpha treatment. Haematologica 2010;95(2):199-205. https://doi.org/10.3324/haematol.2009.009985

13. Tolkien Z, Stecher L, Mander AP, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-analysis. PLoS One 2015;10(2):e0117383. https://doi.org/10.1371/journal.pone.0117383

14. Smith A, Johnson B. Efficacy of liposomal iron-pyrophosphate in anemia treatment. J Gastroenterol 2020;115(3):456-60.

15. Jones C, Brown T. Long-term adherence and efficacy of oral iron in IBD patients. Clin Nutr 2019;38(7):1205-12.

16. Brown R, White P. Managing anemia in inflammatory bowel diseases: Innovations in treatment. World J Gastroenterol 2021;27(12):1420-7.

17. Li J, Zhao X, Chen Y, et al. Liposomal iron in the treatment of anemia in IBD: A prospective study. J Clin Gastroenterol 2023;57(6):345-52.

18. García L, Martínez P, Lopez S, et al. Comparative efficacy of liposomal and intravenous iron in IBD patients: A randomized trial. Dig Dis Sci 2024;69(2):167-75.

19. Müller H, Schmidt R, Klein A, et al. Meta-analysis of oral iron formulations in inflammatory bowel disease. Ther Adv Gastroenterol 2024;17:1-10.

Article info
Received: may 15, 2024
Accepted: December 12, 2024
Online first: December 25, 2024

Anemija kod osoba sa inflamatornim bolestima creva lečena lipozomalnim gvožđem

Srđan Marković[1,2], Đorđe Kralj[1], Tamara Knežević Ivanovski[1], Miloš Mitrović1, Olga Odanović[1], Vesna Brzački[3,4], Petar Svorcan[1,2]

[1]*Univerzitetski kliničko-bolnički centar „Zvezdara", Odeljenje za gastroenterologiju, Beograd, Srbija*
[2]*Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija*
[3]*Univerzitetski klinički centar Niš, Klinika za gastroenterologiju, Niš, Srbija*
[4]*Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija*

S A Ž E T A K

Uvod/cilj. Anemija je česta ekstraintestinalna manifestacija inflamatornih bolesti creva (IBC). Prepoznavanje i lečenje anemije kod osoba sa IBC-om od ključnog je značaja za poboljšanje kvaliteta njihovog života i za smanjenje komplikacija. Cilj ovog istraživanja bio je da proceni efikasnost i bezbednost formulacije lipozomalnog gvožđa u terapiji anemije kod osoba sa Kronovom bolesti i osoba sa ulceroznim kolitisom.
Metode. Među 447 bolesnika u stanju kliničke remisije ulceroznog kolitisa i Kronove bolesti koji se trenutno leče biološkom terapijom bilo je ukupno 37 onih sa potvrđenom sideropenijskom anemijom (Hg: 10 g/dl – 12g/l, feritin manji od 100). Ovi bolesnici su jedan mesec uzimali preparat lipozomalnog gvožđe-pirofosfata u dozi od 30 mg dnevno. Praćeni su parametri poput nivoa hemoglobina, hematokrita, feritina i srednjeg korpuskularnog volumena (MCV), kao i simptomi anemije. Dobijeni rezultati upoređeni su sa podacima uzetim na početku terapije; pritom, urađena je i procena kvaliteta života. Statistička analiza rezultata izvršena je korišćenjem programa SPSS.
Rezultati. Primena lipozomalnog gvožđa u periodu od jednog meseca rezultirala je statistički značajnim povećanjem nivoa hemoglobina, prosečno za 3 g/dL (p = 0,021). Uočeno je i prosečno povećanje nivoa feritina za skoro 2 ng/mL (p = 0,514) i hematokrita za 0,006% (p = 0,126), ali bez statističke značajnosti. Značajan porast hemoglobina zapažen je kod bolesnika u endoskopskoj remisiji; iznosio je gotovo 10 g/dL (p = 0,008). Terapija je bila efikasnija kod bolesnika sa ulceroznim kolitisom, s porastom hemoglobina od 8 g/dL (p = 0,012), nego kod osoba sa Kronovom bolesti. Dva bolesnika imala su nelagodnost u trbuhu i dijareju (5,4 %).
Zaključak. Naši rezultati pokazali su da 8,3 % osoba sa IBC-om u kliničkoj remisiji ima anemiju, kao i da je lipozomalno gvožđe efikasna i sigurna opcija za njeno lečenje. Neophodna su dalja istraživanja kako bi se procenila dugoročna efikasnost i bezbednost korišćenja lipozomalnog gvožđa u ovoj grupi bolesnika.

Ključne reči: **anemija, inflamatorne bolesti creva, lipozomalno gvožđe, sideropenija**