Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
PubMed (National Library of Medicine): ID: (101671502)
Research Article
Volume 8, Issue 4: July-August: 2019, 26-30
ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

CORRELATION BETWEEN MEAN PLATELET VOLUME AND IRON DEFICIENCY ANEMIA

Himanshu Dagor
Sri Aurobindo Institute of Medical Sciences

Article Info: Received 10 July 2019; Accepted 05 August. 2019
DOI: https://doi.org/10.32553/jbpr.v8i4.638
Address for Correspondence: Himanshu Dagor
Conflict of interest statement: No conflict of interest

ABSTRACT:

Background: Iron inhibits megakaryopoiesis so iron deficiency anemia (IDA) leads to microthrombosis. Iron therapy ameliorates thrombocytosis. In this study, we investigated whether young, active, and large platelets are released into peripheral blood during iron treatment. Mean platelet volume (MPV) was measured as an indicator for the presence of these platelets.

Materials and Methods: A total of 80 patients (10 males and 70 females) with IDA were included in this retrospective study. IDA was defined as ferritin level <50 ng/mL with a transferrin saturation <20% or ferritin <15 ng/mL. Daily ferrous sulfate (270 mg iron II sulfate and 80 mg of elemental iron) was given orally to patients. We evaluated retrospectively the hematologic and biochemical parameters prior to and 1 month after iron treatment.

Results: the mean ferritin level of the pretreatment group was 6.5 ± 4.0 ng/mL, MPV was 7.9 ± 1.5 fL, hemoglobin (Hb) was 9.8 ± 1.5 g/dL and the mean cellular volume (MCV) was 71.2 ± 7.2 fL. The mean ferritin level of the posttreatment group was 40.3 ± 15.2 ng/mL, MPV was 8.6 ± 2.0 fL, Hb was 12.5 ± 6.6 g/dL, and MCV was 77.6 ± 5.4 fL. The levels of ferritin ($P < 0.001$), MPV ($P < 0.001$), MCV ($P < 0.001$), and Hb ($P < 0.001$) were significantly higher in the posttreatment group compared to the pretreatment group.

Conclusion: There may be an increase in thrombotic events due to hypercoagulability related to microthrombosis during IDA. Even though thrombosis is corrected during iron treatment, the therapy increases the release of large and active thrombocytes into the peripheral blood.

Keywords: Iron, iron deficiency anemia, mean platelet volume, thrombocytosis, thrombosis

INTRODUCTION

Iron is an essential trace element presents in a number of molecular systems and it is increasingly recognized as an important cofactor for a variety of cell systems.[1] It is the basic element for the production of new red blood cells (RBC). If it is not used in erythropoiesis it is stored as ferritin or hemosiderin.[2] Serum ferritin levels are closely correlated with total body iron stores.[3] Iron deficiency anemia (IDA) occurs due to increased body requirements, insufficient iron supply (depending on dietary iron intake and duodenal absorption) and blood losses.[4] It has been estimated that 30% of the world population suffers from IDA and most of them live in the developing countries.[5] While iron deficiency leads to anemia its excess leads to both deposition of iron in the tissues as hemosiderosis and cellular damage by oxygen radicals as a result of the combination of free iron with peroxides radicals.[6] Excess iron in the body may be dependent on the HFE gene on chromosome 6 as well as it may occur with unnecessary or long-term treatment of iron.[7]

The mean platelet volume (MPV) reflects thrombocyte size. It is an important marker of thrombocyte function. MPV follow-up can be performed by using a low-cost routine hematologic test. When compared to small thrombocytes large ones have more granules and a higher thromboxane A_2 level. They aggregate more rapidly with collagen and express more glycoprotein Ib and IIb/IIIa receptors.[8,9] Thrombocytes secrete many important substances such as coagulation, inflammation, thrombosis, and atherosclerosis mediators that increase the risk of occlusive vascular disease.[10] Previous studies

demonstrated MPV to be associated with both arterial and venous diseases.[11,12]

Iron not only induces erythropoiesis but also suppresses megakaryopoiesis.[13] Small thrombocytes lead to thrombocytosis that occurs in IDA due to not be suppressed megakaryopoiesis.[14] During iron treatment bone marrow production of megakaryocytes can be induced leading to young and large platelets being released into peripheral blood. While iron therapy corrects thrombocytosis and normalizes peripheral thrombocytes it may also lead to release of large thrombocytes into peripheral blood. Iron therapy should be given in caution to patients with thrombosis, heart disease, ischemic stroke. So in this study, we aimed to investigate whether peroral iron treatment is associated with high MPV.

MATERIALS AND METHODS

This retrospective study was carried out in the Internal Medicine Department of Sri Aurobindo Medical College. A total of 80 patients diagnosed with iron deficiency anemia (70 females and 10 males) were included in this study. The mean patient's age was 39.8 ± 15.2 years. Patients with ferritin <50 ng/mL and transferrin saturation <20% or ferritin <15 ng/L were considered iron deficient.[1,15] Peroral ferrous sulfate (270 mg iron II sulfate, 80 mg of elemental iron) was given daily to patients. The patient files were retrospectively analyzed after 1 month of treatment. Exclusion criteria were as follows: folate deficiency, vitamin B_{12} deficiency anemia, or chronic diseases (such as thalassemia, malignancy, active gastrointestinal bleeding, diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, chronic renal failure, and thyroid diseases). Patients were nonsmokers and did not consume alcohol or use drugs (especially drugs that affect iron metabolism).

Laboratory tests

Hematologic tests were performed using the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, Abbott Park, IL, USA). The iron levels, unsaturated iron-binding capacity (UIBC) and biochemical tests were measured by photometric assays using the Abbott Architect C16000 analyzer (Abbott Diagnostics). Ferritin, TSH, and vitamin B_{12} tests (for differential diagnosis) were performed by using the chemiluminescent microparticle immunoassay (CMIA) method by the Abbott Architect I 2000 immunology analyzer (Abbott Diagnostics).

Statistical analysis

The results were reported as the means ± SD. The data analysis was performed using the statistical software SPSS for Windows version 13.1(SPSS, Chicago, IL, USA). All results were analyzed by applying the Kolmogorov-Smirnov test for determining the normal and non-normal data distribution. The differences in all parameters between the pre- and post- treatment groups were analyzed using the paired t-test for those with a normal distribution and Wilcoxon tests for those with a non-normal distribution. The relationships among the variables were analyzed with Pearson's correlation test. Differences were considered significant at $P < 0.05$.

RESULTS

The mean white blood cell count (WBC) of the pretreatment group was 6.3 ± 1.7 ´ 10^9/L, Hb was 9.8 ± 1.5 g/dL, the mean cell volume (MCV) was 71.2 ± 7.2 fL, platelet count (Plt) was 308 ± 98 ´ 10^9/L, MPV was 7.9 ± 1.5 fL, ferritin was 6.5 ± 4.0 ng/mL, and iron was 20.4 ± 10.7 □g/dL. The mean WBC of the posttreatment group was 6.4 ± 1.6× 10^9/L, Hb was 12.5 ± 6.6 g/dL, MCV was 77.6 ± 5.4 fL,Plt was 268 ± 80 ´ 10^9/L, MPV was 8.6 ± 2.0 fL, ferritin was ± 15.2 ng/mL and iron was 45 ± 9.4 □g/dL. The Hb ($P < 0.001$), MCV ($P < 0.001$), MPV ($P < 0.001$) and ferritin ($P < 0.001$) were significantly higher in the post-treatment group. The plt ($P < 0.001$) was significantly lower in the post-treatment group. The demographic characteristics and results of the hematological and biochemical tests are shown in Table 1.

Table 1: The main characteristics and laboratory parameters for the two groups

***N* = 80**	**Before treatment (mean ± SD)**	**After treatment (mean ± SD)**	***P* value**
Age (year)	39.8 ± 15.2		
Gender (M/F)(N)	10/70		
WBC	6.3 ± 1.7	6.4 ± 1.6	0.486

(x10^9/L)			
Hb (g/dL)	9.8 ± 1.5	12.5 ± 6.6	0.001
MCV (fL)	71.2 ± 7.2	77.6 ± 5.4	0.001
Platelet (x10^9/L)	308 ± 98	268 ± 80	0.001
MPV (fL)	7.9 ± 1.5	8.6 ± 2.0	0.001
Ferritin (ng/mL)	6.5 ± 4.0	40.3 ± 15.2	0.001
Fe (□g/dL)	20.4 ± 10.7	45 ± 9.4	0.001
UIBC (ug/dL)	416.9 ± 43.8	348.3 ± 39.7	0.045

M: Male, F: Female,WBC:White blood cells, MCV: Mean cell volume, MPV: Mean platelet volume, Fe: Iron, UIBC: Unsaturated iron binding capacity, FPG: Fasting plasma glucose, BUN: Blood urea nitrogen.

Correlation analysis indicated positive correlations between MCV (r = 0.169, *P* = 0.032) and ferritin (r = 0.156, *P* = 0.015) with MPV. Correlation analysis indicated positive correlations between MCV (r = 0.265, *P* = 0.003), and Hb (r = 0.143, *P* = 0.020) with ferritin.

DISCUSSION

Our data have shown elevation of ferritin, Hb, MCV, and MPV levels following peroral iron treatment in patients with IDA. The increased MPV was correlated with ferritin and MCV. The current study has shown MPV to be increased in patients with IDA taking iron. Iron deficiency is the primary cause of anemia and affects nearly one-quarter of the world population. IDA generally occurs in children due to decreased dietary intake and in young women due to menstruation. Gastrointestinal tract blood loss is the most common cause of IDA occurring in 2-5% of adult males and postmenopausal females in the developed world.[16] In humans intracellular iron is stored as ferritin making this protein important in maintaining iron levels. Hematologic parameters of IDA include: low serum ferritin, low iron, increased total iron binding capacity, increased erythrocytes, protoporphyrin, and increased transferrin binding receptor levels.[17,18] Serum ferritin levels below 12-15 mg/L indicate IDA. In patients with chronic diseases acute phase reactant ferritin <50 ng/L indicates IDA.[1,15]

In our study, posttreatment thrombocyte levels were lower than pretreatment levels. However, MPV increased following the treatment indicating the release of young, large, and active thrombocytes into the peripheral blood stream. In a previous study thrombocytes and MPV levels were compared before and after 8 weeks of oral ferrous sulfate (4 mg/kg/day) in children.[19] Thrombocytes decreased significantly following treatment while MPV increased. Authors reported that thrombocytes increased to normal size after iron therapy. Iron is also an important cofactor for thrombocyte enzyme systems. Iron inhibits thrombocytosis. In patients with IDA thrombocytosis is uninhibited due to low iron and increased IL-6 levels.[20,21] These thrombocytes are smaller than normal. Microthrombocytosis is associated with increased megakaryocytes with less ploidy than normal, an increased megakaryocyte mass, and an increased platelet production rate.[22] In contrast thrombocytopenia of unknown etiology has been reported in patients with severe IDA.[23] Iron treatment may improve thrombocytopenia quickly even though it inhibits megakaryopoiesis. It may increase megakaryopoiesis by stimulating oxidative stress.In the current study MPV was found to be increased even though thrombocytes number decreased following iron therapy. Giles reported that although platelet distribution is normal in pregnancy, patients with preeclampsia and uncomplicated hypertension in late pregnancy tended to have lower platelet counts and larger platelets.[24] Iron treatment may lead to the release of active and large thrombocytes into peripheral blood. Iron stimulation of oxidative stress may lead to increased MPV. Iron inhibition of megakaryocytes may lead to slower and normal or exaggerated maturation. This may lead to the release of active and large thrombocytes.

IDA can cause hypercoagulability, reactive thrombocytosis, anemia, and increased viscosity due to red cell deformability related to microcytosis. It has been reported that thrombosis risk is increased in IDA patients.[25] Previous studies have shown that elevation of collagen and ADP during IDA may lead to increased thrombocyte aggregation.[26] However, other studies have not found increased collagen and ADP during IDA.[27,28] Another study showed that female patients with IDA have normal collagen and ADP levels, but increased menstrual bleeding due to arachidonic-acid- induced platelet dysfunction;[29] iron therapy decreased bleeding in these patients.[19] Alternatively, iron overload may lead to increased platelet aggregation. Excess iron may increase oxidative stress which increases platelet aggregation.[30] In addition to increasing MPV oxidative stress increases proinflammatory cytokines like tumor necrosis factor alpha (TNF-□)

and interlukin-6 (IL6) that stimulate megakaryopoiesis leading to release of active and large thrombocytes.[8] These thrombocytes secrete aggregation-promoting substances such as fibrinogen, collagen, ADP, calcium, and serotonin. Elevated MPV indicates an increase in active and large thrombocytes.[31] Elevated MPV is associated with myocardial infarction, stroke, and arterial and venous thromboembolism.[32] A previous study reported that iron therapy increases fibrin leading to cardiovascular disease.[33] Fibrin is formed from fibrinogen which is released from thrombocytes. Iron therapy leads indirectly to thrombosis and our results indicate increased MPV levels during iron treatment. These findings show that the increased thrombosis risk is related to iron therapy rather than IDA itself. Further studies are needed on this subject. It is known that oxidative stress is increased leading to elevated megakaryopoiesis; iron inhibits megakaryopoiesis which is increased during IDA. However, the release of microthrombocytes into peripheral blood prevents the increase in MPV. Previous studies have shown collagen and ADP to be similar to control groups during IDA. Therefore, thrombosis events with IDA may be related to hyperviscosity.

Limitations of the study

This study included a relatively small sample size with a 1-month follow-up period. During long treatment durations increasing exposure to iron may increase MPV. MPV may be higher with a greater oral dosage or intravenous iron treatment. There are no adequate studies in the literature regarding the relationship between iron treatment and MPV. So there is a need for further studies on this subject.

CONCLUSION

In IDA, there is an increased risk of thrombotic events due to microthrombosis-related hypercoagulability. Although thrombocytosis is improved during iron treatment, the release of large and active thrombocytes into peripheral blood may cause arterial and venous thromboembolism.

REFERENCES

1. Gunawardena S, Dunlap ME. Anemia and iron deficiency in heart failure. Curr Heart Fail Rep 2012;9:319-27.
2. Winter WE, Bazydlo LA, Harris NS. The molecular biology of human iron metabolism. Lab Med 2014;45:92-102.
3. Saito H, Hayashi H, Tomita A, Ohashi H, Maeda H, Naoe T. Increasing and decreasing phases of ferritin and hemosiderin iron determined by serum ferritin kinetics. Nagoya J Med Sci 2013;75:213-23.
4. Busti F, Campostrini N, Martinelli N, Girelli D. Iron deficiency in the elderly population, revisited in the hepcidin era. Front Pharmacol 2014;5:83.
5. Vehapoglu A, Ozgurhan G, Demir AD, Uzuner S, Nursoy MA, Turkmen S, *et al.* Hematological indices for differential diagnosis of Beta thalassemia trait and iron deficiency anemia. Anemia 2014;2014:576738.
6. Roussou P, Tsagarakis NJ, Kountouras D, Livadas S, Diamanti-Kandarakis E. Beta-thalassemia major and female fertility: The role of iron and iron-induced oxidative stress. Anemia 2013;2013:617204.
7. Leao GD, Freire JM, Cunha Fernandes AL, Moura de Oliveira TM, Leão ND, Gil EA, *et al.* Analysis of HFE genes C282Y, H63D, and S65D in patients with hyperferritinemia from northeastern Brazil. J Clin Lab Anal 2014;28:178-85.
8. Cure E, Balik MS, Cumhur Cure M, Guvercin Y, Erkut A, Yuce S, *et al.* Is the mean platelet volume predictive of hip fractures in the elderly? Ann Lab Med 2013;33:367-70.
9. Cure MC, Cure E, Kirbas A, Cicek AC, Yuce S. The effects of Gilbert's syndrome on the mean platelet volume and other hematological parameters. Blood Coagul Fibrinolysis 2013;24:484-8.
10. Demirin H, Ozhan H, Ucgun T, Celer A, Bulur S, Cil H, *et al*. Normal range of mean platelet volume in healthy subjects: Insight from a large epidemiologic study. Thromb Res 2011;128:358-60.
11. Demirkol S, Balta S, Kucuk U, Kucuk HO. Mean platelet volume may be associated with extent of coronary artery disease. Arq Bras Cardiol 2013; 101:284-5.
12. Wan ZF, Zhou D, Xue JH, Wu Y, Wang H, Zhao Y, *et al.* Combination of mean platelet volume and the GRACE risk score better predicts future cardiovascular events in patients with acute coronary syndrome. Platelets 2013.
13. Park MJ, Park PW, Seo YH, Kim KH, Park SH, Jeong JH, *et al.* The relationship between iron parameters and platelet parameters in women with iron deficiency anemia and thrombocytosis. Platelets 2013;24:348-51.
14. Keung YK, Owen J. Iron deficiency and thrombosis: Literature review. Clin Appl Thromb Hemost 2004; 10:387-91.
15. Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I; British Committee for Standards in Haematology. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol 2013;161:639-48.
16. Hug BL, Tichelli A, Benkert P, Stirnimann G, Schifferli JA. Diagnosis and treatment of iron deficiency in medical inpatients at a Swiss tertiary university referral hospital: A retrospective observational cohort

study of clinical practice. Swiss Med Wkly 2013; 143:13847.

17. van Tellingen A, Kuenen JC, de Kieviet W, van Tinteren H, Kooi ML, Vasmel WL. Iron deficiency anaemia in hospitalised patients: Value of various laboratory parameters. Differentiation between IDA and ACD. Neth J Med 2001;59:270-9.
18. Worwood M. The laboratory assessment of iron status — an update. Clin Chim Acta 1997;259:3-23.
19. Kürekçi AE, Atay AA, Sarící SU, Zeybek C, Köseoğlu V, Ozcan O. Effect of iron therapy on the whole blood platelet aggregation in infants with iron deficiency anemia. Thromb Res 2000;97:281-5.
20. Przybyszewska J, Zekanowska E, Kędziora-Kornatowska K, Boinska J, Cichon R, Porzych K. Serum prohepcidin and other iron metabolism parameters in elderly patients with anemia of chronic disease and with iron deficiency anemia. Pol Arch Med Wewn 2013;123:105-11.
21. Kadikoylu G, Yavasoglu I, Bolaman Z, Senturk T. Platelet parameters in women with iron deficiency anemia. J Natl Med Assoc 2006;98:398-402.
22. Bluteau O, Langlois T, Rivera-Munoz P, Favale F, Rameau P, Meurice G, *et al*. Developmental changes in human megakaryopoiesis. J Thromb Haemost 2013;11:1730-41.
23. Morris VK, Spraker HL, Howard SC, Ware RE, Reiss UM. Severe thrombocytopenia with iron deficiency anemia. Pediatr Hematol Oncol 2010;27:413-9.
24. Giles C. The platelet count and mean platelet volume. Br J Haematol 1981;48:31-7.
25. Maguire JL, deVeber G, Parkin PC. Association between iron-deficiency anemia and stroke in young children. Pediatrics 2007;120:1053-7.
26. Tekin D, Yavuzer S, Tekin M, Akar N, Cin S. Possible effects of antioxidant status on increased platelet aggregation in childhood iron-deficiency anemia. Pediatr Int 2001;43:74-7.
27. Polette A, Blache D. Effect of vitamin E on acute iron load-potentiated aggregation, secretion, calcium uptake and thromboxane biosynthesis in rat platelets. Atherosclerosis 1992;96:171-9.
28. Yıldırım ZK, Orhan MF, Büyükavcı M. Platelet function alterations and their relation to P-selectin (CD62P) expression in children with iron deficiency anemia. Blood Coagul Fibrinolysis 2011;22:98-101.
29. Akay OM, Akin E, Mutlu FS, Gulbas Z. Effect of Iron Therapy on Platelet Function among Iron-Deficient Women with Unexplained Menorrhagia. Pathophysiol Haemost Thromb 2008;36:80-3.
30. Pratico D, Pasin M, Barry OP, Ghiselli A, Sabatino G, Iuliano L, *et al.* Iron- dependent human platelet activation and hydroxyl radical formation: Involvement of protein kinase C. Circulation 1999; 99:3118-24.
31. Gear AR, Suttitanamongkol S, Viisoreanu D, Polanowska-Grabowska RK, Raha S, Camerini D. Adenosine diphosphate strongly potentiates the ability of the chemokines MDC, TARC, and SDF-1 to stimulate platelet function. Blood 2001;97:937-45.
32. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: The Tromso Study, Tromso, Norway. J Thromb Haemost 2010;8:157-62
33. Lipinski B, Pretorius E. Iron-induced fibrin in cardiovascular disease. Curr Neurovasc Res 2013; 10:269-74.