ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 6, Issue – 1, February - 2023, Page No. : 202 - 210

Evaluation of Cardiac Function in Iron Deficiency Anemia before and after Total Dose Iron Therapy

[1]Dr. Rishikesh Malokar, Ex Senior Resident.

[2]Dr. Dhirendra Yadav, Assistant Professor, Department of Medicine, LTMMC and Gen Hospital, Sion, Mumbai.

[3]Dr. Rupal Padhiyar, Associate Professor, Department of Medicine, LTMMC and Gen Hospital, Sion Mumbai.

[4]Dr. Swati Chavan, Professor, Department of Medicine, LTMMC and Gen Hospital, Sion, Mumbai.

Corresponding Author: Dr. Swati Chavan, Professor, Department of Medicine, LTMMC and Gen Hospital, Sion Mumbai.

How to citation this article: Dr. Rishikesh Malokar, Dr. Dhirendra Yadav, Dr. Rupal Padhiyar, Dr. Swati Chavan, "Evaluation of Cardiac Function in Iron Deficiency Anemia before and after Total Dose Iron Therapy", IJMACR- February - 2023, Volume – 6, Issue - 1, P. No. 202 – 210.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Objectives: Anemia is quite prevalent worldwide with iron deficiency contributing to more than 50% of it. It causes significant circulatory changes like increased cardiac output, heart rate.

Cardiovascular changes of anemia can be reversed to certain extent by correcting iron deficiency with total dose iron therapy. The present study was undertaken to evaluate cardiac function in Iron Deficiency anemia, before and after total dose iron therapy.

Methods: This was a prospective observational study conducted on 46 patients with iron deficiency anemia. Patient's clinical profile, laboratory parameters, imaging features (cardiomegaly on chest X-ray and echocardiography) as well as electrocardiography findings were noted initially and on follow up at 12 weeks after total dose iron therapy.

Results: Out of 46 patients, maximum patient were in the age group of 21-30 years with of patients being females. The mean average values for pulse rate was 103.48+11.9 beats per min, systolic blood pressure was 111.87+10.48 mmHg, diastolic blood pressure was 69.74+9 mmHg, haemoglobin was 4.99+1.24 g/dl. Chest X-ray showed cardiomegaly of anemic patients which reduced to post anemia correction (P value<0.001).

Electrocardiography showed ST-segment depression, left axis deviation and T-wave inversion which normalized after anemia correction. patients received intravenous ferric carboxymaltose and 17 (37%) patients received iron sucrose as total dose iron therapy along with oral iron therapy.

Conclusion: Anemia correction significantly improves clinical symptoms and cardiac functional as well as

maladaptive structural changes measured on echocardiography as evident in our study. Ferric carboxymaltose is a safe and convenient option for IDA treatment.

Keywords: Iron deficiency anemia, Total dose iron therapy, Echocardiography.

Introduction

Iron deficiency is the commonest nutritional deficiency worldwide, affecting more than one-third of the population. World Health Organization (WHO) estimate for 2019, mentions that there are about two billion people (27% world population) with anemia in the world and half of the anemia is due to iron deficiency. Anemia is one of the major public health problems in India, with about 68.4% children and 64.4% women suffering from anemia as per NFHS-5 survey (2019).

Anemia significantly alters circulatory dynamics through increased preload, cardiac output decreased after load, positive chronotropic effects and changes in cardiac geometry (compensatory remodelling) as a consequence to sustained hemodynamic and volume overload. Diastolic and systolic LV chamber sizes increase to accommodate this greater output. In cases of mild to moderate anemia, hemodynamic adaptations permit adequate cardiovascular compensation. The transition from a high output (compensated) cardiac state to a state of LV dysfunction (decompensated) appears to begin at a hemoglobin level of approximately 7 g/dL in the iron deficient patient. As the haemoglobin drops to less than 5 g/dL, LV function drops drastically.2

Echocardiography is a valuable non-invasive diagnostic test for the assessment of cardiovascular system. Echocardiography parameters useful for assessment of cardiac dysfunction in anemia are Left Ventricular Ejection Fraction (LVEF), left ventricular volume (LVIDd, LVIDs, IVST), Cardiac output (CO= HR x SV). The ratio of end systolic wall stress to end systolic volume index (ESS/ESVI) has also been used to evaluate cardiac contractility. This ratio is reduced suggesting functional compromise in patients with severe anemia with hemoglobin less than 6 g/dL. Again the EF and FS which are considered to be indices of systolic function, being lower in anemic patients may indicate that the systolic function in these patients is slightly compromised2. Cardiomyopathy associated with iron deficiency is reversible. When the anemia is corrected, the LV hypertrophy decreases, LV function improves. Hence it is important to correct iron deficiency anemia at the earliest to prevent worsening of heart functions.

Various studies have proven the beneficial effects of Total Dose Iron (TDI) therapy on improvement in cardiac function (regression of left ventricular hypertrophy), exercise capacity and overall decrease adverse outcomes in patients with congestive heart failure.3It has been proven that in stable, symptomatic, ambulatory patients with chronic heart failure, an impaired left ventricular ejection fraction, and iron deficiency, treatment with ferric carboxymaltose (FCM) over a 24-week period improves symptoms, physical performance, and the quality of life even before there was a significant rise in hemoglobin level. Longer follow-up of 1 year in patients treated with FCM with its good safety profile and tolerability has a demonstrated significantly reduced risk of hospital admission due to worsening HF. This proves the theory that correction of the electrophysiological abnormalities of the heart in iron deficiency patient by TDI therapy may be the result of correction of iron at the tissue level.4

Hence the present study was undertaken to correlate changes in echocardiography parameters before and after

Total dose iron (TDI) therapy in iron deficient anemic patients.

Aims & Objectives

1. To study ECG and Echocardiography changes in iron deficiency anemia patients.
2. Correlation of various echo changes with hemoglobin level.
3. To study changes on ECG and echocardiography after correction of Iron deficiency anemia with TDI therapy.

Materials and Methods

This was a prospective observational study conducted over a period of 18 months on patients with iron deficiency anemia, attending medicine OPD and/or admitted in medicine wards in a tertiary care Centre of Mumbai. Patients meeting inclusion criteria were serially recruited by random sampling after taking written informed consent. Study was conducted after approval from Institutional Ethics Committee.

Inclusion Criteria

1. Patients attending medicine OPDs or admitted in medicine wards with hemoglobin <7gm% (according to WHO criteria).
2. Microcytic, Hypochromic blood picture in peripheral smear.
3. Red cell indices suggestive of iron deficiency anemia.
4. Patients who are planned to receive TDI.

Exclusion Criteria

1. Anemia with other etiological diagnosis.
2. Patients who did not give valid consent
3. Cardiac Dysfunction due to other etiology (IHD, HTN, DM, Hypothyroid, alcoholism, Tuberculosis, HIV)

Patients with iron deficiency anemia were enrolled after fulfilling the inclusion and exclusion criteria and giving written informed consent. Age and sex-matched 10 healthy non-anemic patients were enrolled as control.

Detailed history was taken for all patients, which included history of palpitation, chest pain, breathlessness and swelling of legs and other symptoms like easy fatigability, generalized weakness and black stools. The clinical examination included pulse, blood pressure, pedal edema, heart sounds, murmurs heard, liver and spleen size and features of congestive heart failure.

All patients underwent a complete Hema tological examination and peripheral smear examination. Estimation of serum iron, TIBC, %saturation, serum ferritin was done in all cases. Other investigations like TSH, HIV Eliza, lipid profile, RBS were done. Standard 12 lead electrocardiogram was recorded for all patients in the resting state. Echocardiography was done for all the patients.

Echocardiography: Transthoracic Echocardiography was done using Sonolyte Envisor using 3.5 and 5MHz transducer, probe by experienced cardiologist. All patients were examined in left lateral supine position. Measurements of the LV cavity dimensions were derived from M-mode recordings and were made according to the recommendations of the American Society of Echocardiography (ASE) at end diastole and end systole. Systolic LV function was evaluated by the ejection fraction.

Left: ventricular volumes and subsequently, stroke volume, ejection fraction and cardiac output were estimated by the method of discs, following ASE recommendations and using apical 2- and 4-chamber views.

Echocardiography parameters studied were

- Inter ventricular septum thickness at end diastole and end systole (IVSTd &IVSTs),

- Left ventricular inner dimension at end diastole and end systole (LVIDd &LVIDs),
- Left Ventricular Ejection Fraction (LVEF),
- Stroke volume
- Cardiac output (CO) was calculated as CO=HR x SV.

All patients received blood transfusion, total iron correction in the form of parenteral iron and oral iron supplementation. Total Iron deficit was calculated as 2.4 x Hb deficit x Weight+500(reserve). In parenteral iron therapy patients received either Injection Iron sucrose or Injection Ferric carboxymaltose (FCM) as per hospital availability and patient's affordability.

Ferriccarboxymaltose was the preferred choice due less chances of infusion related and other adverse reactions and single dose of infusion most of the time. Follow up of patients were done by personal telephonic contacts. They were called every 4-6 weeks for routine check-up. At end of 12weeks all Hema tological parameters, ECG and echocardiography were repeated.

Statistical Methods and Data Analysis

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) were used for continuous variables, frequencies and percentages were calculated for categorical Variable. Comparisons of mean of various quantitative variables were analysed using unpaired t test and Paired t test respectively for unpaired and paired data.

Results and Observations

A total of 46 anemic patients meeting the inclusion criteria were enrolled in the study conducted over a period of 18 months. 10 non-anemic healthy (age and sex matched) patients were taken as controls.

Table 1 is showing the comparison of demographic characteristics and dietary patterns between cases and controls. In this study, out of 46 patients, 16 (34.8%) cases were in 21-30 age group followed by 11 (23.9%) in <20 years of age, 10 (21.7%) in <40 years of age and 9 (19.6%) in 31-40 years age group. Most of the patients (67.34%) were females and had mixed dietary pattern (78.3%).

Figure 1 is showing various clinical symptoms and signs of anemia. The most common symptoms on presentation were palpitation (71.7%) and generalised weakness (60.9%) followed by easy fatigability (58.7%), breathlessness (56.5%), angina (34.8%), black stools (23.9%) and pedal edema (21.8%). All the patients had pallor on examination followed by systolic murmur (21.7%), organomegaly (4.3%), icterus (2.2%), edema (2.2%) and basal crepitations (2.2%).

Table 2 is showing comparison of mean and standard deviation of various clinical and laboratory parameters between cases and controls. On clinical examination the mean pulse in anemic patients was 103.48 (+11.9) beats per min with range of 76-128, whereas the mean systolic blood pressure was 111.87mmHg (+10.48) and mean diastolic blood pressure was 69.74mmHg (+ 9).

Laboratory investigations of patients showed mean hemoglobin of 4.99 g/dl (+1.24), Red blood cell count of 1.99 million/µl (+0.38), haematocrit of 15.71 % (+4.13), MCV of 58.24fl (+6.62), MCH of 21.46pg (+3.12) and MCHC of 24.24 g/dl (+3.35).

Iron studies have shown mean serum iron level of 23.05 mcg/dl (+10.87), TIBC of 490.81mcg/dl (+51.99), serum ferritin of 6.33 ng/dl (+2.61) and % transferring saturation of 4.67% (+2.01).

Table 3 is showing before and after anemia correction comparison of cardiomegaly on Chest X-ray & various ECG Parameters.

Above table reveals that incidence of cardiomegaly was 63.04% which reduced to 21.73% after anemia correction. This is statistically significant with p value <0.001 and odds ratio 6.1.

This tables shows that mean heart rate in anemia cases was 103 with SD of 12.02, which reduced to mean heart rate of 92 after correction which is statistically significant with p value of <0.001. Out of 46, 9cases (19.6%) had left axis deviation in ECG which reverted normal axis in 6 of them. This improvement is also statistically significant with p value <0.001. Other findings includes T inversion in % patients (10.9%) and ST depression in 10 patients (21.7%) which reverted back to normal after treatment, this is also statistically significant.

Table 4 is showing Comparison of 2D ECHO Parameters before and after anemia Correction.

This tables shows correlation analysis between all echocardiography parameters before and after therapy. Change in values of IVST s, LVID d, LVIDs, LVEF, SV, CO were statistically significant with p=0.012, p=<0.001, p=0.006, p=<0.001, p=0.001, p=<0.001 respectively.

As per our data analysis there is significant decrease left ventricular inner dimensions. Mean LVIDd at presentation was 48.24mm with SD of 3.69mm and this reduced to mean of 45.61mm with SD of 2.14mm after therapy. Same statistically significant decrease was seen in LVIDs, from 30.51mm to 30.01mm.

The mean EF before treatment was 58.35 % with SD of 5.16 %. It improved to mean EF of 64.53% with SD of 4.61 %. This data table also showed that mean SV significantly decreased from 80.57ml with SD 11.38ml before therapy to 71.85ml with SD of 7.39ml after therapy. Cardiac output was also significantly reduced from 8307.4 ml/min pre-therapy to 6624 ml/min post treatment.

Figure 3 is showing various types of treatment received by the patients of iron deficiency anemia. In this study total 41cases (89.1%) received blood transfusion either one or two units. All the cases received parenteral iron corrections either iron sucrose or ferric carboxymaltose. Out of 46 cases, 17 (37%) received iron sucrose and 29 (63%) received ferric carboxymaltose. All the patients received oral iron supplementation.

Discussion

Our study was conducted to know the various effects of iron deficiency anemia on cardiac function, both on presentation and after total dose iron therapy. It was conducted on 46 patients of iron deficiency anemia over a period of 18 months along with 10 patients (age and sex matched non-anemic healthy individuals) taken as control for the study.

Majority of our anemic patients (78.26%) were young (<40 years age) with a mean age of 30.5 years. 67.34% of the patients were females probably due to higher incidence of iron deficiency in them. This finding was similar with the study done by Alvares JF and colleagues in 30 anemic patients, out of which 19 (63.33%) were females and 11 were males with mean age of 30 years.4

In our study most common clinical symptoms observed were palpitation (71.7%), generalized weakness (60.9%), easy fatigability (58.7%) & breathlessness (56.5%) whereas the most common sign on examination was pallor seen in all 46 patients. Other examination findings noted were systolic murmur (21.7%), organomegaly (4.3%), icterus (2.2%), pedal edema (2.2%) and basal

crepitations (2.2%). Similar finding of functional systolic murmur on examination was observed in studies done by Athanasios Aessopos et al and G C Gupta.5, 6

Mean pulse rate was 103 beats per minute whereas mean systolic blood pressure was 120 mmHg and diastolic blood pressure was 70 mmHg in our study which were similar in the study done by Farquana Qushnood in 31 anemic patients. 3

Cardiomegaly on chest X-ray, which is common findings in anemia was seen in 63.04% of our patients which subsequently decreased to 21.73% after correction of anemia. The findings are consistent with the study by Nikita Hegde n et al in which they found that between one third and two thirds of patients with severe anemia had cardiomegaly on chest radiography, and the cardiac silhouette returned to normal within a few weeks of the resolution of anemia.2

Significant changes were observed post-therapy in laboratory parameters like haemoglobin which increased from 4.9 g/dl (mean) to 11 g/dl and serum iron level which increased from 23 mg/dl pre-therapy to 98 mg/dl 3 months post treatment. A Korean study done by In-Jeong Cho et al had shown similar findings.7

Electrography (ECG) changes noted in our study were sinus tachycardia with mean heart rate of 103, ST segment depression (21.70%), left axis deviation (19.60%) and T wave inversion (10.90%) which almost totally resolved 3 months after treatment with ECG showing heart rate of 92, left axis deviation only in 6.5% without any ST segment depression or T wave inversion which was statistically significant. In a study done on 21 patients with iron deficiency anemia, Mustafa Tuncer et. al. have shown that mean heart rate was higher on 24 hour Holter monitoring in anemic patients compared to control.8 Study done by Alvares et al showed mean heart rate on the ECG changed from 102.66 pre-therapy to 93.4 post-therapy was consistent with our study. 4Mehta et alfound a significantly high incidence of abnormal ST segment depression in an exercise test in IDA compared to the control group which got corrected within 2-3 days of IV iron therapy, before a significant rise in hemoglobin level, suggests the causal relation between tissue iron deficiency and abnormal ST segment response.9

In our study we analysed changes between various echocardiography parameters before and after iron therapy and there correlation with laboratory parameters. There was significant decrease in mean Left ventricular internal diameter at end systole(LVIDs) of 48.24mm and Left ventricular internal diameter at end diastole (LVIDd) of 30.51mm pre-therapy to 45.61mm and 30.01mm respectively post-therapy with iron. Similar findings were observed in study conducted by Stritzke J et.al, Takahashi M et.al and JF Alvares et.al, signifying that increase in LVIDs seen in anemic patients are the long-term results of volume overload (hyperdynamic state) leading to cardiac enlargement which can be reversed with iron correction.10, 11, 4

Ejection Fraction (EF) which is the indicator of systolic function of heart had significantly improved from mean 58.35% before therapy to mean 64.53% after therapy in our study. There was no significant correlation of EF with serum haemoglobin, iron and ferritin level. Our findings are consistent with the study by Farquana Qushnood and colleagues. 3Study done by Balfour et al reported that EF was significantly decreased in patients with sickle cell anemia.13

An increase in Stroke Volume (SV) is an important determinant of high cardiac output in chronic anemia, because it corresponds with severity of anemia. Our

study has shown a significant decrease in mean SV from 80.57ml pre-therapy to 71.85ml post-therapy. A study by RB Panwar et al. 1991 also showed that stroke volumes were higher in anemic patients when compared with healthy controls. 14The negative correlation of SV and hemoglobin levels in anemic patients may be attributed to hyperdynamic state in chronic anemia which causes an increased LV preload and lower after load.

In our study cardiac output (CO) was also significantly reduced from 8307.4 ml pre therapy to 6624 ml post treatment. Study done by Bahl VK et al. and Schafer GE et al showed consistent findings as our study. 15, 16There were no statistically significant correlation between CO and serum iron, haemoglobin and ferritin level in the present study.

Study strength

Our study has shown that it is possible to improve clinical features and cardiac maladaptive structural changes with anemia correction.

Limitations of the study

It was single center study with small sample size and thus the findings cannot be generalized to general population unless multicentric study with large sample size is conducted.

Conclusion

Iron deficiency anemia is quite prevalent in younger population with significant adverse effect on cardiac structure and function. Prompt and adequate correction of anemia can significantly improve clinical features and reverse cardiac maladaptive changes like cardiomegaly, electrocardiographic changes as well as echocardiographic abnormalities to a great extent. TDI therapy with ferric carboxymaltose is safe and convenient treatment option for IDA.

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Legend Tables

Table 1: Comparison of Demographic profile and dietary patterns between cases and controls

Parameter	Group	
	Cases (n=46) n (%)	Controls (n=10) n (%)
Age (in Years)		
≤20	11(23.9)	1(10.0)
21-30	16(34.8)	5(50.0)
31-40	9(19.6)	3(30.0)
>40	10(21.7)	1(10.0)
Gender		
Male	15(32.66)	5(50.0)
Female	31(67.34)	5(50.0)
Diet		
Mixed	36(78.3)	7(70.0)
Veg	10(21.7)	3(30.0)

Table 2: Comparison of descriptive statistics of different clinical and laboratory parameters between cases and controls

Parameter	Group	
	Cases(n=46) Mean (SD)	Controls(n=10) Mean (SD)
Age (Years)	30.50(12.95)	29.20(6.84)
Weight (kg)	55.24(7.85)	61.60(6.85)
Pulse	103.48 (11.90) Max-128 Min-76	79.20(13.34) Max-92 Min-62
SBP	111.87 (10.48)	117.80(9.25)
DBP	69.74(9.00)	74.80(10.79)
Hb	4.99 (1.24)	12.46(1.10)
TLC	6766(1978)	6555(1500)
Platelets (Lac)	4.65 (1.11)	3.01 (0.85)
RBCCount	1.99 (0.38)	5.46 (0.54)
HCT	15.71(4.13)	37.38(3.31)
MCV	58.24(6.62)	87.6(4.08)
MCH	21.46(3.12)	29.3(0.82)
MCHC	24.24(3.35)	31.80(1.03)
Retit Count	0.879(1.79)	0.30 (0.10)
Serum Iron	23.05(10.87)	100.60 (13.12)
TIBC	490.81 (51.99)	268(31.55)
%Saturation	4.67 (2.01)	37.90(5.97)
Serum Ferritin	6.33 (2.61)	44.80(8.66)

Table 3: Before and after anemia Correction comparison of Cardiomegaly on Chest X-ray & various ECG Parameters (N=46)

Parameter	Before Treatment N (%)	After Treatment N (%)	P Value
Cardiomegaly on Chest X-Ray			
Present	29(63.04%)	10(21.73%)	<0.001

Absent	17(36.95%)	36(78.26%)	
Chi square test, ODDSratio6.1			
ECG Parameters			
HeartRate – Mean(SD)	103(12.02)	92 (9.31)	<0.001
Axis Deviation (LAD)	9 (19.6)	3 (6.5)	<0.001
T Inversion	5 (10.9)	0	0.040
ST Depression	10 (21.7)	0	<0.001

Table 4: Comparison of 2D ECHO Parameters before and after Anemia Correction (N=46)

Parameter	Group		PValue
	Before (n=46) Mean (SD)	After(n=46) Mean (SD)	
IVSTd(mm)	9.44 (0.57)	9.45 (1.55)	0.981
IVSTs(mm)	8.07 (0.52)	8.17 (0.51)	0.012
LVIDd(mm)	48.24(3.69)	45.61(2.14)	<0.001
LVIDs(mm)	30.51(1.74)	30.01(1.77)	0.006
LVEF (%)	58.35(5.16)	64.53(4.61)	<0.001
SV (ml)	80.57(11.38)	71.85(7.39)	<0.001
CO (ml/min)	8307.4(1442.4)	6624.5(915.5)	<0.001

Figure 1: Presenting symptoms of anemia

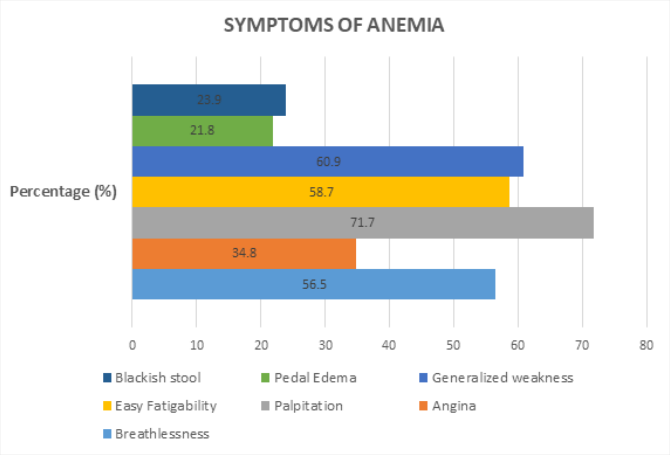

Figure 2: general and systemic examination findings in anemia

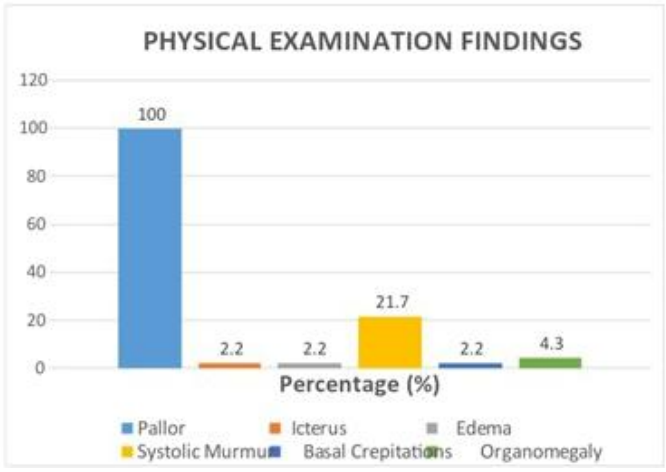

Figure 3: Distribution of anemia cases according to Treatment