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Research Article

HOW ARE CARDIAC FUNCTIONS ALTERED IN PEDIATRIC PATIENTS RECEIVING ORAL IRON SUPPLEMENTATION DUE TO ANEMIA?

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ABSTRACT

Objective: This study aims to investigate whether oral iron supplementation improves structural and functional alterations by evaluating the echocardiography and electrocardiography findings of the pediatric patients with iron deficiency anemia.

Methods: This is a prospective review of 30 pediatric patients who were diagnosed with iron deficiency anemia and received 12-week-long iron supplementation at the study center. All children underwent hematological workup, detailed echocardiography examination and electrocardiography evaluation at the time of diagnosis for iron deficiency anemia and the end of 12-week-long iron treatment.

Results: After 12-week-long iron treatment, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, red blood cell count, Mentzer index, serum iron, serum iron binding capacity, serum ferritin and transferrin increased significantly (p=0.001, p=0.001, p=0.001, p=0.036, p=0.001, p=0.002, p=0.001 and p=0.001 respectively). Pulse rate, respiration rate, and diastolic left ventricle wall thickness decreased significantly while tricuspid E and A wave velocities increased significantly at the end of iron supplementation (p=0.004, p=0.033, p=0.009, p=0.003 and p=0.021 respectively). As for the tissue Doppler echocardiography findings, only interventricular septum isovolumetric contraction time decreased significantly after iron treatment (p=0.002). The PR interval shortened significantly, p dispersion decreased significantly and T-peak to T-end interval shortened significantly following iron supplementation (respectively p=0.013, p=0.033 and p=0.029).

Conclusion: Oral iron supplementation seems to contribute to the reversal of cardiac remodeling, elimination of compensatory hemodynamic mechanisms and inhibition of sympathetic activation within cardiac tissues.

Keywords: *Child, Echocardiography, Electrocardiography, Iron Deficiency Anemia*

1. INTRODUCTION

Anemia is defined as a decrease in the number of red blood cells and hemoglobin (Hb) concentration in blood (DeLoughery, 2017). Iron deficiency is the most common cause of anemia which occurs due to the lack of iron intake and/or depletion of iron stores in the body (Camaschella, 2015). Being the most abundantly found trace element in human body, iron is required to produce Hb and transport oxygen (Subramaniam & Girish, 2015). Iron deficiency is a global health problem and a common medical condition which is frequently encountered in daily clinical practice (Lopez et al., 2016). It has been reported that iron deficiency affects 30–40% of pre-school children in industrialized countries, and nearly all children at pre-school age in developing countries (Wang, 2016).

World Health Organization estimated that nearly half of the children worldwide aged 0–5 years between 1993 and 2005 had anemia (McLean et al., 2009). In order to make a diagnosis of iron deficiency anemia in children, lowered Hb concentrations, ferritin levels and/or reticulocyte counts should be measured depending on age, sex, pregnancy, altitude, and smoking (Powers & Buchanan, 2014). The physiologic response to anemia is a compensatory elevation in cardiac output by increasing blood volume, preload, heart rate, and stroke volume. These alterations can be identified with the augmentation in sympathetic nervous activity (Yokusoglu et al., 2007).

The symptoms and signs of iron deficiency anemia that result from hypoxic functioning include fatigue, breathlessness at rest, exertional dyspnea, vertigo, syncope, headache, tachycardia, and cardiac systolic flow murmurs (Anand & Gupta, 2018). In severe cases, patients might have dyspnea at rest, angina pectoris, and hemodynamic instability (Anand & Gupta, 2018; Yokusoglu et al., 2007). Accordingly, it has been speculated that ongoing acceleration in sympathetic nervous activity of the heart might even lead to cardiomyopathy (Hegde et al., 2006).

This study aims to investigate whether oral iron supplementation improves structural and functional alterations by evaluating the echocardiography and electrocardiography findings of the pediatric patients with iron deficiency anemia.

2. METHODS

This is a prospective review of 30 pediatric patients who were diagnosed with iron deficiency anemia and received 12-week-long iron supplementation at the Department of Pediatrics in Afyonkarahisar Health Sciences University Hospital between January 2019 and March 2019. The study cohort consisted of 9 boys (30%) and 21 girls (70%) and their mean age was 14.2 ± 3.1 years (range: 7-18 years). This study was approved by the Institutional Review Board and Ethical Committee of the study center.

The inclusion criteria were being a pediatric patient aged less than 19 years and having a diagnosis of iron deficiency anemia. The pediatric patients with other types of anemia, other hematologic diseases, infections, cardiac diseases, renal diseases, gastrointestinal system diseases, endocrinopathies and malignancies were excluded. The children who used drugs impairing iron absorption, pediatric patients who had iron treatment or anti-inflammatory treatment previously and children who failed to get regular iron treatment were excluded.

Data related with age, height, body weight, pulse rate, respiration rate, peripheral capillary oxygen saturation, systolic and diastolic blood pressures were recorded. Body mass index was computed as follows: Body mass index= Weight (kg) / Height^2 (m^2)

2.1. Laboratory Studies

Complete blood count was made, serum concentrations of iron, ferritin and transferrrin were measured and total iron binding capacity (TIBC) was specified at the time of diagnosis for iron deficiency anemia and the end of 12-week-long iron treatment.

Complete blood count was made by using daily calibrated hemocytometer (LH-780, Beckman Coulter, USA). Measurements of Hb, mean erythrocyte volume (MCV), mean corpuscular Hb concentration (MCHC), red blood cell distribution width (RDW), red blood cell count, white blood cell count and platelet count were made. In order to distinguish iron deficiency anemia from beta-thalassemia, Mentzer index was calculated as MCV per red blood cell count.

A calibrated Dimension RxL Max Integrated Chemistry System was used to measure serum concentrations of iron, ferritin and transferrin (Siemens Healthineers, Erlangen, Germany). TIBC was directly determined by IL TestTM TIBC Sample Pretreatment Kit (Instrumentation Laboratory SpA, Milano, Italy; Cat. No 181730–00).

2.2. Echocardiography Examination

Echocardiography examination was performed by means of a commercially available machine with 3-5 MHz transducers (Vivid I, GE Healthcare, Chicago, IL, USA). The patients were made to rest for 5 minutes before the measurements and breathe slowly throughout the procedure. Recordings were performed with subjects in the supine or left lateral positions. All children underwent M-mode, two-dimensional, color, Doppler-continuous, and pulse wave-echocardiography examination at the time of diagnosis and the end of iron treatment. The mean values were recorded by averaging the results of three consecutive measurements.

M-mode tracings were supplied at the level of the tips of mitral leaflets in the parasternal long-axis position, and measurements of the left ventricular end-systolic and end-diastolic dimension were performed according to the recommendations of the American Society of Echocardiography (Nagueh et al., 2016). Left ventricular end-systolic and end-diastolic dimensions as well as aorta and interventricular septum dimensions were measured from the parasternal long-axis window. Left ventricular ejection fraction and fractional shortening were provided using Teichholtz in M-mode echocardiography.

Tissue Doppler measurements were performed to designate the myocardial velocities during systole, early diastole and late diastole. The isovolumic contraction time (IVCT) was the time period between the end of the myocardial wave during late diastole (Am) and the beginning of the myocardial wave during systole (Sm). The isovolumic relaxation time (IVRT) was the time period between the end of the Sm wave and the beginning of the myocardial wave during early diastole (Em). Ejection time was the duration of ventricular outflow. Myocardial performance index (MPI) was the sum of IVCT and IVRT values, divided by ejection time.

2.3. Electrocardiography Evaluation

All children had electrocardiography (ECG) at the time of diagnosis and the end of iron treatment. The 12-lead ECG was saved at a paper speed of 50 mm/hour and gain of 10 mm/mV (Cardiofax V; Nihon Kohden Corporation, Tokyo, Japan) in the supine position. The patient was allowed to breathe spontaneously, but speaking was not permitted during the recording. All measurements were done manually by using magnifying glass and the mean values were recorded by averaging the results of three consecutive measurements.

The electrical axis of the heart in the frontal plane was represented by the QRS-axis. P-wave duration was measured in lead II, from the beginning to the end of P-wave. PR interval was also measured in lead II, from the beginning of P-wave to the beginning of R-wave. QRS complex duration was measured in lead V, from the beginning of Q wave to the end of the S wave. The measurement of the QT interval was started from the onset of the QRS complex until the end of the T-wave. Corrected QT interval was specified by Bazett's formula (Bazett, 1920). P-wave dispersion was calculated by subtracting minimum P-wave duration from maximum P-wave duration. QRS dispersion was the difference between maximum and minimum QRS complex durations. Corrected QT dispersion was found by subtracting minimum corrected QT interval from maximum corrected QT interval.

2.4. Statistical Analysis

Collected data were analyzed by Statistical package for Social Sciences version 25.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) and categorical variables were denoted as numbers or percentages. Kolmogorov-Smirnov test was used to test the distribution of variables. Paired samples t-test and Wilcoxon test were used for the comparisons. Two-tailed p values less than 0.05 were accepted to be statistically significant.

3. RESULTS

Table 1 shows the clinical characteristics of the patients before and after 12-week-long iron administration. The height and weight of the patients increased significantly but the pulse rate and respiration rate decreased significantly following iron supplementation ($p=0.002$, $p=0.014$, $p=0.004$ and $p=0.033$ respectively).

Table 1. Clinical characteristics before and after iron supplementation

	Before treatment (n=30)	After treatment (n=30)	p
Height (m)	1.56±0.16	1.58±0.15	0.002*
Weight (kg)	49.0±15.7	50.3±15.2	0.014*
Body mass index (kg/m^2)	19.67±4.13	19.77±3.90	0.631
Arterial oxygen saturation (%)	97.0±2.0	97.5±1.4	0.340
Pulse rate (beats/min)	97.6±17.5	86.6±10.3	0.004*
Respiration rate (breaths/min)	23.8±2.5	22.4±2.1	0.033*
Systolic blood pressure (mmHg)	108.3±9.9	105.3±8.5	0.177
Diastolic blood pressure (mmHg)	69.3±8.7	66.3±6.7	0.163

*p<0.05 was accepted to be statistically significant.

After 12-week-long iron treatment, hemoglobin, MCV, MCHC, red blood cell count, Mentzer index, serum iron, TIBC, ferritin and transferrin values increased significantly (p=0.001, p=0.001, p=0.001, p=0.036, p=0.001, p=0.002, p=0.001 and p=0.001 respectively). On the contrary, RDW, Mentzer index and platelet count decreased significantly (p=0.001, p=0.004 and p=0.006 respectively) (Table 2).

Table 2. Hematological parameters before and after iron supplementation

	Before treatment (n=30)	After treatment (n=30)	p
Hemoglobin (g/dl)	9.97±1.28	12.7±1.54	0.001*
Mean corpuscular volume (fl)	72.45±7.83	82.15±8.25	0.001*
Mean corpuscular hemoglobin concentration (g/dl)	29.31±1.67	31.5±1.42	0.001*
Red blood cell count (x10^3/mm^3)	4645.0±549.5	4836.7±434.2	0.036*
Red cell distribution width (%)	17.28±2.56	15.26±2.60	0.001*
Mentzer index (MCV/RBC count)	15.84±2.69	17.18±2.63	0.004*
White blood cell count (/mm3)	6942.3±2292.5	7334.7±2179.6	0.277
Neutrophil/Lymphocyte	2.32±1.13	2.17±1.10	0.430
Platelet count (x10^3/mm3)	339.570±105.827	302.370±62.924	0.006*
Serum iron (mg/dl)	27.50±9.33	66.58±38.85	0.001*
Serum iron binding capacity (µg/dl)	419.64±60.32	383.73±53.33	0.002*
Serum ferritin (ng/ml)	6.42±5.24	23.62±24.34	0.001*
Serum transferrin	6.76±2.71	17.69±10.0	0.001*

*p<0.05 was accepted to be statistically significant

Table 3. Echocardiography findings before and after iron supplementation

	Before treatment (n=30)	After treatment (n=30)	p
Systolic interventricular septum thickness (mm)	1.58±0.79	1.40±0.33	0.243
Diastolic interventricular septum thickness (mm)	0.97±0.19	0.95±0.20	0.655
Systolic left ventricle internal diameter (mm)	2.30±0.52	2.43±0.58	0.257
Systolic left ventricle posterior wall thickness (mm)	1.66±0.35	1.69±0.35	0.658
Diastolic left ventricle internal diameter (mm)	4.12±0.61	4.24±0.56	0.208
Diastolic left ventricle posterior wall thickness (mm)	1.12±0.21	0.99±0.23	0.009*
Systolic volume (mm^3)	53.83±20.92	59.73±18.11	0.103
End-diastolic volume (mm^3)	75.23±25.60	81.63±24.66	0.112
Fractional shortening (%)	44.40±7.61	44.43±8.47	0.985
Ejection fraction (%)	76.50±8.67	75.13±8.88	0.492
Systolic left ventricle mass (g)	138.45±45.38	146.66±62.0	0.254
Systolic left ventricle mass index (g/m)	98.78±28.16	100.08±39.12	0.860
Diastolic left ventricle mass (g)	163.73±58.98	157.46±73.26	0.462
Diastolic left ventricle mass index (g/m)	116.68±34.30	106.71±37.97	0.241
Systolic left ventricle outflow tract (m/sec)	1.32±0.20	1.33±0.24	0.597
Diastolic left ventricle outflow tract (m/sec)	1.20±0.55	1.25±0.68	0.157
Ascending aorta (mm)	1.39±0.20	1.34±0.27	0.243
Descending aorta (mm)	1.44±0.17	1.46±0.38	0.761
Mitral E velocity	0.99±0.21	0.99±0.23	0.919
Mitral A velocity	0.67±0.16	0.63±0.17	0.379
Mitral E/A	1.50±0.28	1.85±1.79	0.297
Tricuspid E velocity	0.67±0.15	0.81±0.25	0.003*
Tricuspid A velocity	0.43±0.10	0.50±0.16	0.021*
Tricuspid E/A	1.62±0.47	1.66±0.4	0.599
Deceleration time (sec)	83.40±30.38	85.93±15.54	0.669
Tricuspid annular plane systolic excursion	3.86±0.81	3.92±0.79	0.618
Mitral annular plane systolic excursion	3.19±0.63	3.36±0.59	0.188

*$p<0.05$ was accepted to be statistically significant.

Table 3 summarizes the echocardiography findings of the patients before and after iron treatment. Diastolic left ventricle wall thickness decreased significantly while tricuspid E and A wave velocities increased significantly at the end of iron supplementation (p=0.009, p=0.003 and p=0.021 respectively). As for the tissue Doppler echocardiography findings, only interventricular septum IVCT decreased significantly after 12-week-long iron administration (p=0.002) (Table 4).

Table 4. Tissue doppler echocardiography findings before and after iron supplementation

	Before treatment (n=30)	After treatment (n=30)	p
Left ventricle			
Em	0.1993±0.0378	0.2067±0.0706	0.543
Am	0.0830±0.0177	0.0887±0.0391	0.491
Sm	0.1140±0.0275	0.1360±0.1264	0.359
Interventricular relaxation time	62.77±11.72	57.90±9.38	0.055
Interventricular contraction time	60.63±8.38	58.97±11.34	0.365
Myocardial performance index	48.42±7.99	45.74±7.93	0.230
Interventricular septum			
Em	0.1403±0.0281	0.1417±0.0232	0.830
Am	0.1027±0.1512	0.0723±0.0148	0.288
Sm	0.0857±0.0119	0.0850±.0128	0.827
Interventricular relaxation time	60.07±13.19	63.0±10.48	0.290
Interventricular contraction time	67.03±10.61	58.13±8.9	0.002*
Myocardial performance index	50.52±10.78	47.76±7.67	0.227
Right ventricle			
Em	0.1747±0.0386	0.1720±0.0295	0.677
Am	0.1230±0.0295	0.1210±0.0264	0.774
Sm	0.1507±0.0393	0.1483±0.0231	0.798
Interventricular relaxation time	61.07±14.28	58.47±14.16	0.396
Interventricular contraction time	64.03±13.62	63.47±1.50	0.832
Myocardial performance index	52.45±10.95	49.41±11.40	0.218

*p<0.05 was accepted to be statistically significant.

Table 5 displays the ECG findings of the patients before and after 12-week-long iron treatment. The PR interval shortened significantly, p dispersion decreased significantly and T-peak to T-end interval shortened significantly following iron supplementation (respectively p=0.013, p=0.033 and p=0.029).

Table 5. Electrocardiography findings before and after iron supplementation

	Before treatment (n=30)	After treatment (n=30)	p
Heart rate (beats/min)	86.57±16.49	77.47±14.21	0.480
Heart axis (°)	48.50±25.08	34.27±19.38	0.050
P wave (sec)	110.67±31.40	94.0±20.44	0.928
PR interval (sec)	188.0±38.09	171.33±26.09	0.013*
QRS interval (sec)	108.0±27.04	79.33±24.34	0.118
QT interval (sec)	364.67±32.24	377.33±35.12	0.612
Corrected QT interval (sec)	436.67±47.74	424.73±32.31	0.682
P dispersion	62.66±22.73	40.33±20.40	0.033*
QRS dispersion	64.67±44.47	35.33±15.25	0.340
Corrected QT dispersion	62.07±30.18	66.10±22.95	0.337
T-peak to T-end interval (sec)	80.33±23.85	56.33±22.97	0.029*

*p<0.05 was accepted to be statistically significant.

4. DISCUSSION

Anemia is a consequence of long term iron deficiency which leads to compensatory changes in circulation (Hegde et al., 2006). At the beginning of iron deficiency anemia, cardiac output increases and circulation is enhanced. Long-lasting hyperdynamic circulation increases the load on the heart and causes myocardial ischemia and hypoxia (Hegde et al., 2006; Jankowska & Ponikowski, 2010).

In case iron deficiency anemia is not treated, myocardium cannot overcome the high load and, thus, ventricular walls are thickened and ventricles become hypertrophic and dilated (Cohen-Solal et al., 2014; Jankowska & Ponikowski, 2010). Remodeling of cardiac muscles is a long term complication of iron deficiency anemia. This complication usually ends up with the development of mechanisms for hemodynamic compensation (Cohen-Solal et al., 2014; Jankowska & Ponikowski, 2010). These mechanisms include (i) reduced afterload due to a decrease in systemic vascular resistance, (ii) increased preload due to acceleration in venous return and (iii) increased left ventricular function triggered by increased sympathetic activity and inotropic factors. In addition, heart rate is increased in anemic patients due to hypoxia-stimulated chemoreceptors (Cohen-Solal et al., 2014; Hegde et al., 2006; Jankowska & Ponikowski, 2010).

It has been reported that left ventricle volume index is decreased, cardiac index is reduced, left ventricle end diastolic pressure is increased, left atrium is enlarged and left ventricle diastolic filling parameters are extended significantly in patients with iron deficiency anemia (Simsek et al., 2010). A Turkish study also pointed out significantly elevated myocardial performance indices of left ventricle, right ventricle and interventricular septum in infants with iron deficiency anemia. Additionally, ejection time was significantly lowered in left ventricle, right ventricle and interventricular septum in these infants (Alioglu et al., 2013).

Anemia may cause abnormalities in sympathetic nerve activity due to the perception of hypoxia in the carotid body (Kobak et al., 2019). Turner et al. established a model of iron deficiency in mice and found that the increase in cardiac output triggered the activation of sympathetic nervous system within the heart and ultimately resulted in left ventricular hypertrophy (Turner et al., 2002). Similarly, Yokusoglu et al. demonstrated the impairment in autonomic nervous system of the heart in patients with iron deficiency anemia (Yokusoglu et al., 2007). It has been hypothesized that hypoxia inhibits mitochondrial respiratory chain or potassium channels and, thus, intracellular calcium accumulates. The accumulation of calcium in myocardial cells subsequently impairs the myocardial functions (Kobak et al., 2019; Turner et al., 2002; Yokusoglu et al., 2007).

The PR interval is defined as the time interval from the onset of the p wave to the start of the QRS complex. This interval reflects the conduction through the atrioventricular node (Schumacher et al., 2017; Simsek et al., 2010). P wave dispersion is described as the difference between the widest and the narrowest p wave duration recorded from all of the ECG leads. P wave dispersion has been addressed as a marker for atrial remodeling and predictor for atrial fibrillation (Okutucu et al., 2016; Pérez-Riera et al., 2016). Increased p wave dispersion designates the delay in intra-atrial and inter-atrial conduction time which can be attributed to the lack of a well-coordinated conduction system within the atrial muscles (Okutucu et al., 2016; Pérez-Riera et al., 2016; Schumacher et al., 2017). T-peak to T-end interval is depicted as an index for transmural dispersion of ventricular repolarization. Any prolongation in this interval has been considered as a risk factor for ventricular tachyarrhythmia (Dinshaw et al., 2018; Tse et al., 2018). A Turkish study determined that heart rate was significantly higher and maximum P wave duration and P wave dispersion were

significantly longer in patients with iron deficiency anemia when compared to healthy controls (Simsek et al., 2010).

Previously published studies have revealed the effects of iron treatment on exercise capacity and life quality of the adults with heart failure (Anker et al., 2009; Ponikowski et al., 2015; van Veldhuisen et al., 2017). In the FAIR-HF study, intravenous ferric carboxymaltose treatment significantly improved clinical symptoms, functional capacity and quality of life in patients with heart failure (Anker et al., 2009). The CONFIRM-HF study attested that intravenous iron treatment over a 1-year period helped to maintain the improvements in functional capacity, clinical symptoms, and quality of life in heart failure patients (Ponikowski et al., 2015). The EFFECT-HF study designated the beneficial effects of intravenous iron supplementation on mixed venous oxygen tension of the adults with heart failure (van Veldhuisen et al., 2017). A meta-analysis confirmed that intravenous iron supplementation is a safe and efficient treatment approach which is associated with a recovery in quality of life parameters, reduction in hospitalizations, and prolongation of six minute walk distance (Avni et al., 2012).

To the best of our knowledge, this is the first study to investigate how the echocardiography and electrocardiography findings are altered in pediatric patients who received oral iron supplementation for the treatment of iron deficiency anemia. In this study, diastolic left ventricle wall thickness decreased significantly, tricuspid E and A wave velocities increased and interventricular septum IVCT decreased significantly in children who received oral iron supplementation for 12 weeks. Moreover, The PR interval shortened significantly, p dispersion decreased significantly and T-peak to T-end interval shortened significantly following iron supplementation.

5. LIMITATIONS OF THE STUDY

The power of the present study is limited by several factors such as relatively small cohort size, relatively short follow up time and absence of a healthy control group.

6. CONCLUSION

The findings of the present study imply that oral iron supplementation contributes to the reversal of cardiac remodeling, elimination of compensatory hemodynamic mechanisms and inhibition of sympathetic activation within cardiac tissues. Further research is warranted to clarify the effects of iron supplementation on cardiac functions of the pediatric patients diagnosed with iron deficiency anemia.

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