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The Effect of Iron Therapy on Electrocardiography Parameters in Children with Iron Deficiency Anemia

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Abstract

Background: Iron is essential for hemoglobin (Hb) production and the body's ability to transport oxygen. This study aimed to evaluate the impact of iron deficiency anemia (IDA) on electrocardiographic (ECG) parameters in children.

Materials and Methods: This pre–post interventional study was carried out at Ali Asghar Hospital in Zahedan and included children aged 5 to 18 years diagnosed with IDA. For each participant, hematologic markers Hb, ferritin, serum iron, and total iron-binding capacity (TIBC) were assessed. In addition, ECG indices, including P wave duration (PWd), QT interval dispersion (QTd), corrected QT interval (QTc), Tp-e interval, and Tp-e dispersion, were recorded both at baseline and after three months of iron therapy.

Results: A total of 45 children (mean age: 11.47 ± 4.00 years) participated in the study. After three months of treatment with 4–6 mg/kg/day of elemental iron, significant improvements were observed in several hematological and ECG parameters, including ferritin, serum iron, TIBC, P wave duration, P wave dispersion, QTc, QTc dispersion, Tp-e interval, Tp-e dispersion, and the Tp-e/QTc ratio ($p < 0.001$). In children with Hb levels between 10 and 11 g/dL, all ECG parameters improved significantly ($p < 0.001$), while those with Hb levels between 8 and 9 g/dL showed significant improvement in all parameters except the Tp-e/QTc ratio ($p = 0.002$). Among children with ferritin levels >10 ng/mL, all ECG parameters improved ($p < 0.001$), whereas in those with ferritin ≤10 ng/mL, all but QTc showed significant changes ($p = 0.002$). Serum iron levels between 15 and 20 µg/dL were associated with improvements in all evaluated parameters ($p = 0.002$), while those with levels between 21 and 28 µg/dL demonstrated significant changes only in TIBC and P wave duration ($p = 0.002$).

Conclusion: The study concluded that the Iron supplementation positively impacts hematological and ECG parameters, supporting heart health in children**.**

Keywords: Children, Electrocardiography, Iron Deficiency Anemia

Introduction

Iron plays a crucial role in the synthesis of hemoglobin (Hb) and is vital for transporting, delivering, and utilizing oxygen throughout the body (1). Iron deficiency anemia (IDA) is defined by Hb levels falling below the 5th percentile of the age-specific normal range, primarily due to insufficient iron reserves.

Many studies use a Hb cutoff of around 11 g/dL, which corresponds to roughly two standard deviations below the average, to diagnose IDA. This condition is the most common type of anemia and often results from poor dietary iron intake or depletion of the body's iron stores (2).

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Iron deficiency is the most common dietary abnormality globally, affecting a significant proportion of the population, with prevalence rates ranging from low levels in highly developed nations to much higher levels in less developed regions (3). Studies such as Mantadakis et al., (4) indicate that the prevalence of iron deficiency ranges from 3% to 48%. In Eastern Europe, the prevalence of IDA can reach up to 50% among various age groups, while in Western Europe, it remains below 5%. Additionally, it is estimated that up to 40% of preschool children in low- and middle-income countries are iron deficient and/or IDA. When this percentage is 27.7% among Iranian children under the age of six, boys constituted the majority (5). A reduction in the quantity of red blood cells and the concentration of Hb in the blood is known as anemia (6). Hemoglobin, myoglobin, the generation of oxygen radicals, and a number of essential bodily processes all depend on anemia (1-6).

Half of all anemias are caused by IDA, which is the most frequent cause of anemia. Roughly 9% of infants between the ages of 12 and 36 months are iron deficient, and among them, anemia affects one-third of the children (2). One of the most frequent reasons of the hyperdynamic condition of the heart at rest is anemia, which affects all of the organs, including the heart. It affects the heart by reducing the myocardium's O_2 supply, which leads to a mismatch in the supply and demand of the heart, which can result in myocardial ischemia or infarction (3). According to Alnuwaysir et al., (7) the clinical spectrum of IDA can vary from producing left ventricular dysfunction to being asymptomatic. The connection between anemia and cardiovascular disease has received attention. Anemia is intimately linked to increased oxidative stress and chronic inflammation. It can also lead to left ventricular hypertrophy, activate the sympathetic nervous system, and stimulate the renin-angiotensin-aldosterone system (8). Besides causing left ventricular dysfunction, IDA has been associated with various electrocardiographic (ECG) changes. These may include sinus tachycardia, T wave abnormalities, disturbances in atrioventricular conduction, as well as premature supraventricular and ventricular beats (9). Left ventricular systolic and diastolic dysfunction have been studied in pediatric anemia populations, despite the paucity of information on the subject. However, a recent study has improved understanding of the pathophysiological mechanisms of various diseases that cause ventricular arrhythmias and sudden cardiac death. Previous studies have shown that in individuals with iron deficiency, certain ECG markers related to atrial depolarization and ventricular repolarization specifically P wave dispersion (PWd) and QT dispersion (QTd)—may serve as predictors for the onset of atrial and ventricular arrhythmias (9). In addition to QT and QTc dispersions, new parameters that are generated from the 12-lead surface ECG have also been identified as markers of transmural dispersion of repolarization. These parameters include the Tp-e interval and Tp-e dispersion, which measure the time interval between the peak and the end of the T wave (10). It has never been done before to assess ventricular repolarization heterogeneity parameters such as QT, QTc dispersions, Tp-e interval, and Tp-e dispersion in otherwise healthy children with low iron levels. Showed how iron deficiency anemia affects the Tp-e interval and QTc duration in females, and since they were shortened, iron deficiency anemia may be ruled out as the reason of prolonged Tp-e and QTc. More sizable, prospective, randomized trials are required to ascertain the connection between cardiac occurrences and transmyocardial and regional repolarization parameters. If left untreated, IDA can worsen cardiac

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conditions and may even result in arrhythmia (11). Therefore, the proper treatment for anemia due to iron deficiency, able to reduce the incidence of heart problems. This study aimed to assess the effect of Iron therapy on ECG parameters in children with Iron deficiency anemia.

Materials and Methods

Design and population

This pre-post treatment study was conducted on 45 children with iron deficiency anemia (IDA) at Ali Asghar Hospital in Zahedan, Iran between 2020 and 2021. In the study Convenience sampling was used to recruit participants from those who met specific criteria.

Criteria

The inclusion criteria required participants to be pediatric patients aged from 5 to 18 years old with a diagnosis of IDA. It's noteworthy to mention the specific Hb thresholds used to IDA: below 13 g/dL for boys and below 12 g/dL for girls. Exclusion criteria included children presenting with alternative forms of anemia, other hematologic disorders, active infections, congenital or acquired cardiac conditions, renal pathologies, gastrointestinal diseases, endocrinopathies, or malignancies were excluded from the study. Furthermore, participants were not eligible if they had a history of medications known to interfere with iron absorption, had previously received iron supplementation or anti-inflammatory therapies, or demonstrated noncompliance with the prescribed iron treatment regimen.

Sample size

For a nonparametric Wilcoxon Signed-Rank paired test, the sample size is estimated using the following formula (12).

$N= (Z_{\alpha/2+} Z_{\beta})^2/4(P-0.5)^2$

In the sample size calculation, we used a z-score for the significance level $\alpha=0.05$, corresponding to $Z\alpha/2=1.96$ and $Z_{\beta} =0.84$. In this formula p=0.74 that will give us approximately 45 children.

Treatment

The typical dosage of ferrous sulfate, Tablet 200 mg with the 50 mg elemental Iron (Made in Iran, DaruPakhsh) that used 4-6 mg of elemental iron per kilogram of body weight per day, divided into 2 doses in 3 months. Ferrous sulfate is best to be taken with empty stomach to optimize absorption, but if gastrointestinal discomfort arises, it can be consumed with a small amount of food. It is important to avoid taking it alongside dairy products, calcium supplements, or antacids, as these can hinder iron absorption. Hemoglobin levels and serum ferritin checked monthly to monitor the treatment's effectiveness. Additionally, potential side effects, such as gastrointestinal issues like constipation or nausea, monitored and managed through dietary adjustments or alternative formulations if was necessary.

Blood Sample Collection and Measurements

To accurately diagnose and monitor IDA in children, the following hematological parameters of Hb, ferritin, serum iron, and total iron-binding capacity (TIBC) measured before starting treatment. The treatment lasted for three month and after that these measurements repeated.

A total of 5mL of blood collected to ensure sufficient volume for all required tests of Hb, ferritin, serum iron, and total iron-binding capacity. To determine the concentration of Hb in the blood, collect 0.5 to 1 mL of whole blood in an EDTA tube. Follow the laboratory procedure for Hb measurement, which typically involves using a hematology analyzer or Hb assay kit according to the manufacturer's instructions. Record the Hb concentration as an indicator of anemia. To measure ferritin concentration, 0.5 to 1 mL of blood will be collected in a serum separator tube. The blood will be allowed to clot for about

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30 minutes at room temperature. Following this, the tube will be centrifuged at 1500-2000 x g for 10-15 minutes to separate the serum. The serum will then be carefully transferred into a clean, labeled container. A ferritin assay kit or an automated immunoassay analyzer will be used according to the manufacturer's instructions to measure the ferritin concentration, which will be recorded in nanograms per milliliter (ng/mL).To measure the concentration of iron in the blood serum, indicating the amount of circulating iron bound to transferrin, collect 0.5 to 1 mL of blood in a serum separator tube. Allow the blood to clot for about 30 minutes at room temperature, then centrifuge the tube at 1500-2000 x g for 10-15 minutes to separate the serum. Carefully transfer the serum into a clean, labeled container. Use a serum iron assay kit or an automated biochemical analyzer according to the manufacturer's instructions and record the serum iron concentration in micrograms per deciliter (µg/dL). To measure the maximum amount of iron that can be bound by proteins in the blood, primarily transferrin, collect 0.5 to 1 mL of blood in a serum separator tube. Allow the blood to clot for about 30 minutes at room temperature, then centrifuge the tube at 1500-2000 x g for 10-15 minutes to separate the serum. Carefully transfer the serum into a clean, labeled container. Use a TIBC assay kit or an automated biochemical analyzer according to the manufacturer's instructions and record the TIBC value.

Electrocardiography

At both the initial diagnosis and following iron therapy, each participant underwent a standard 12-lead ECG. Recordings were performed with the patient lying supine, using a Cardiofax V (Nihon Kohden Corporation, Tokyo, Japan), at a paper speed of 50 mm/s and a calibration of 10 mm/mV. Throughout the procedure, children were instructed to remain still, breathe normally, and refrain from speaking to avoid artifacts.

ECG parameters were measured manually with the aid of a magnifying glass to enhance accuracy. For each parameter, three consecutive beats were analyzed, and their average value was recorded.

P-wave duration was evaluated in lead II, measured from its onset to its termination. P-wave dispersion was determined by the difference between the longest and shortest P-wave durations observed across the leads. The QT interval was identified as the interval from the beginning of the Q wave to the end of the T wave, and its corrected value (QTc) was calculated using Bazett's formula. QT dispersion (QTd) was derived from the variation between the maximum and minimum QT intervals, while corrected QT dispersion was obtained similarly using QTc values.

For Tp-e interval assessment, the measurement extended from the T-wave peak to its end, defined as the intersection of the tangent to the descending limb of the T wave with the isoelectric line. U waves, when present, were not included in the analysis. Finally, the Tp-e/QTc ratio was calculated using Tp-e intervals measured from the precordial leads.

Ethical Considerations

The study received approval from the Ethics Committee of Zahedan University of Medical Sciences, Iran (Ethics Code: IR.ZAUMS.REC.1399.373). It was also registered in the Iranian Registry of Clinical Trials under the number IRCT20250416065355N.

Statistical Methods

Data analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The normality of the continuous variables was assessed using the Shapiro–Wilk test, which showed that the data were not normally distributed. Therefore, the Wilcoxon signed-rank test, a nonparametric approach, was used to

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compare measurements before and after treatment. A p-value below 0.05 was considered statistically significant.

Results

The children in the study aged from 5 to 18 years with the mean of 11.47±4.00 years. The gender distribution was 23(51.1%) and 22(48.9%) in girls and boys respectively. Table I presents the mean and standard deviation of various blood measures and electrocardiogram (ECG) parameters before and after the treatment. From the table revealed all blood measures increased except TIBC and all the ECG parameters decreased after the treatment.

The results of the Wilcoxon paired test for non-normally distributed data are presented in the Table II, indicating that pre- and post-treatment measurements of ferritin, serum Iron, TIBC, P wave, P wave dispersion, QTc, QTc dispersion, Tpe, and Tpe dispersion had a statistically significant improvement ($p < 0.001$) after the treatment. TPe/QTc also shows a statistically significant difference ($p < 0.001$). Overall, the treatment appears to have a positive effect on the measured biomarkers and electrocardiographic parameters in children with iron deficiency anemia.

The results of the Wilcoxon paired test of hematological and electrocardiogram measures based on two different groups of Hb are presented in the Table III. In the 10<= Hb<=11 category all the parameters had statistically significant difference ($p < 0.000$) before and after the treatment. For the 8<= Hb<=9 category, all parameters except TPe/QTc show a statistically significant difference ($p < 0.002$). For most parameters such as TIBC, P wave, P wave dispersion, QTc dispersion and Tpe, the Negative Ranks are slightly higher in the $8 \leq Hb \leq 9$ group compared to the $10 \leq Hb \leq 11$ group,. For QTC, there is no difference in Negative Ranks between the two groups. For Tped and TPe/QTC, the Negative Ranks are higher in the $10 \leq Hb \leq 11$ group compared to the $8 \leq Hb \leq 9$ group. This comparison highlights that, except for Tpe dispersion and TPe/QTc, the Negative Ranks tend to be higher in the $8 \leq Hb \leq 9$ group.

The results of the Wilcoxon paired test of hematological and electrocardiogram measures based on two different groups of ferritin are presented in the Table IV. The table shows that all parameters in the Ferritin>10 category have a statistically significant difference ($p < 0.001$) before and after the treatment. For the Ferritin<=10 category, all parameters except QTc show a statistically significant difference ($p < 0.002$). Overall, the treatment appears to have a positive effect on all of the electrocardiography parameters especially for the Ferritin<=10 category. However, the effect of treatment on TIBC, P wave, and the direction of the change for TPe/QTc is inconclusive for the Ferritin>10 category. For the most ECG parameters such as P wave, P wave dispersion, QTc dispersion and Tpe, the Negative Ranks are significantly higher in the Ferritin ≤ 10 group compared to the Ferritin > 10 group. For QTc, there is still a notable difference in Negative Ranks, with a difference of 8. For Tped and TPe/QTc, the differences are smaller but still significant. This comparison highlights that the Negative Ranks tend to be higher in the Ferritin ≤ 10 group for all ECG parameters, suggesting a more pronounced change in the negative direction in this group compared to the Ferritin > 10 group.

Table V showed that all ECG parameters in the $15 \leq$ serum iron ≤ 20 category and TIBC and P wave in the $21 \leq$ serum iron ≤ 28 category exhibited statistically significant differences ($p < 0.0021$) before and after treatment. Overall, the treatment appeared to have a positive effect on most

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of the measured electrocardiographic parameters in children with iron deficiency anemia, particularly in the $15 \leq$ serum iron ≤ 20 group. For most parameters (TIBC, P wave, P wave dispersion, QTc dispersion, and Tp-e), the Negative Ranks were significantly higher in the $21 \leq$ serum iron ≤ 28 group compared to the $15 \leq$ serum iron ≤ 20 group. For QTc, a notable difference in Negative Ranks was observed, and for Tp-e dispersion and Tp-e/QTc, the differences were even larger. This comparison highlighted that the Negative Ranks were consistently higher in the $21 \leq$ serum iron ≤ 28 group for all ECG parameters, suggesting a more pronounced change in the negative direction in this group compared to the $15 \leq$ serum iron ≤ 20 group.

Table VI showed that all ECG parameters except Tp-e dispersion in the TIBC < 440 category, and TIBC and P wave in the TIBC ≥ 440 category, demonstrated statistically significant differences ($p = 0.003$) before and after treatment. The treatment appeared to have a positive effect on most of the measured electrocardiographic parameters in children with iron deficiency anemia, especially in the TIBC < 440 category. The comparison results highlighted higher Negative Ranks in the TIBC ≥ 440 group for all ECG parameters, indicating a more pronounced change in the negative direction in this group compared to the TIBC < 440 group.

Table I: Mean and standard deviation of blood's measures and ECG's parameters

Variables	Treatment	Mean	SD
Hemoglobin	Pre	9.27	0.91
	Post	11.13	1.36
Ferritin	Pre	10.38	2.12
	Post	79.47	31.93
Serum Iron	Pre	21.42	3.63
	Post	58.98	13.38
TIBC	Pre	449.78	25.12
	Post	298.36	33.26
P wave	Pre	98.13	5.29
	Post	73.82	10.17
P dispersion	Pre	34.24	3.28
	Post	24.91	4.75
QTC	Pre	456.29	8.93
	Post	403.29	17.84
QTcd	Pre	59.73	6.60
	Post	45.22	9.79
Tpe	Pre	98.98	4.19
	Post	77.42	10.61
Tped	Pre	36.89	3.94
	Post	21.82	6.91
Tpe / QTC	Pre	0.22	0.01
	Post	0.19	0.02

TIBC : Total Iron Binding Capacity, P-wave: duration from the beginning to the end of the P-wave , P wave d: maximum P-wave duration- minimum P-wave duration, QT interval: started from the onset of the Q wave to the end of the T wave, QTc: was calculated using Bazett's formula ,QTd: Difference between the longest and shortest QT intervals ,QTCd: maximum QTc interval - minimum QTc interval, Tpe interval: measured from the peak of the T wave (highest point) to the end of the T wave, Tped: maximum Tpe interval - minimum Tpe interval.

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Table II: Blood measures and electrocardiographic parameters before and after Intervention in children with IDA

Parameter	Negative Ranks	Positive Ranks	Ties	Z*	p
Hemoglobin	0	39	6	-5.501	<0.001
Ferritin	0	45	0	-5.842	<0.001
Serum Iron	0	45	0	-5.843	<0.001
TIBC	45	0	0	-5.842	<0.001
P WAVE	45	0	0	-5.843	<0.001
P dispersion	43	2	0	-5.800	<0.001
QTC	45	0	0	-5.842	<0.001
QTcd	44	0	1	-5.786	<0.001
Tpe	45	0	0	-5.843	<0.001
Tped	45	0	0	-5.845	<0.001
TPe/QTC	40	5	0	-5.300	<0.001

*: Wilcoxson test, TIBC : Total Iron Binding Capacity, P-wave: duration from the beginning to the end of the P-wave , P wave d: maximum P-wave duration- minimum P-wave duration, QT interval: started from the onset of the Q wave to the end of the T wave, QTc: was calculated using Bazett's formula ,QTd: Difference between the longest and shortest QT intervals ,QTCd: maximum QTc interval - minimum QTc interval, Tpe interval: measured from the peak of the T wave (highest point) to the end of the T wave, Tped: maximum Tpe interval - minimum Tpe interval.

Table III: Electrocardiographic parameters before and after intervention for Hb categorization in children with IDA

	8<= Hb<=9					10<= Hb<=11				
After-Before	Negative Ranks	Positive Ranks	Ties	Z	P	Negative Ranks	Positive Ranks	Ties	Z	P
TIBC	23	0	0	-4.2	<0.001	22	0	0	-4.109	<0.001
P WAVE	22	1	0	-4.172	<0.001	21	1	0	-4.061	<0.001
P dispersion	23	0	0	-4.198	<0.001	22	0	0	-4.109	<0.001
QTC	22	0	1	-4.154	<0.001	22	0	0	-4.11	<0.001
QTcd	23	0	0	-4.202	<0.001	22	0	0	-4.109	<0.001
Tpe	23	0	0	-4.207	<0.001	22	0	0	-4.11	<0.001
Tped	19	4	0	-3.163	0.002	21	1	0	-4.074	<0.001
TPe/QTC	19	4	0	-3.163	0.002	21	1	0	-4.074	<0.001

*: Wilcoxson test, Total Iron Binding Capacity, P-wave: duration from the beginning to the end of the P-wave , P wave d: maximum P-wave duration- minimum P-wave duration, QT interval: started from the onset of the Q wave to the end of the T wave, QTc: was calculated using Bazett's formula ,QTd: Difference between the longest and shortest QT intervals ,QTCd: maximum QTc interval - minimum QTc interval, Tpe interval: measured from the peak of the T wave (highest point) to the end of the T wave, Tped: maximum Tpe interval - minimum Tpe interval.

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Table IV: Electrocardiographic parameters before and after intervention for ferritin categorization in children with IDA

	Ferritin<=10					Ferritin>10				
After-Before	Negative Ranks	Positive Ranks	Ties	Z	P	Negative Ranks	Positive Ranks	Ties	Z	P
TIBC	27	0	0	-4.543	<0.001	18	0	0	-3.726	<0.001
P WAVE	26	1	0	-4.522	<0.001	17	1	0	-3.662	<0.001
P dispersion	27	0	0	-4.541	<0.001	18	0	0	-3.725	<0.001
QTC	26	0	1	-4.48	<0.001	18	0	0	-3.727	<0.001
QTcd	27	0	0	-4.543	<0.001	18	0	0	-3.725	<0.001
Tpe	27	0	0	-4.546	<0.001	18	0	0	-3.725	<0.001
Tped	23	4	0	-3.772	<0.001	17	1	0	-3.68	<0.001
TPe/QTC	23	4	0	-3.772	<0.001	17	1	0	-3.68	<0.001

*: Wilcoxson test Total Iron Binding Capacity, P-wave: duration from the beginning to the end of the P-wave , P wave d: maximum P-wave duration- minimum P-wave duration, QT interval: started from the onset of the Q wave to the end of the T wave, QTc: was calculated using Bazett's formula ,QTd: Difference between the longest and shortest QT intervals ,QTCd: maximum QTc interval - minimum QTc interval, Tpe interval: measured from the peak of the T wave (highest point) to the end of the T wave, Tped: maximum Tpe interval - minimum Tpe interval.

Table V: Electrocardiographic parameters before and after intervention for iron serum categorization in children with IDA

	15<=Iron serum <=20					21<=Iron serum <=28				
After-Before	Negative Ranks	Positive Ranks	Ties	z	p	Negative Ranks	Positive Ranks	Ties	z	p
TIBC	18	0	0	-3.727	<0.001	27	0	0	-4.544	<0.001
P WAVE	17	1	0	-3.683	<0.001	26	1	0	-4.508	<0.001
P dispersion	18	0	0	-3.724	<0.001	27	0	0	-4.541	<0.001
QTC	17	0	1	-3.665	<0.001	27	0	0	-4.544	<0.001
QTcd	18	0	0	-3.727	<0.001	27	0	0	-4.542	<0.001
Tpe	18	0	0	-3.728	<0.001	27	0	0	-4.544	<0.001
Tped	14	4	0	-2.591	0.010	26	1	0	-4.469	<0.001
TPe/QTC	14	4	0	-2.591	0.010	26	1	0	-4.469	<0.001

Total Iron Binding Capacity, P-wave: duration from the beginning to the end of the P-wave , P wave d: maximum P-wave duration- minimum P-wave duration, QT interval: started from the onset of the Q wave to the end of the T wave, QTc: was calculated using Bazett's formula ,QTd: Difference between the longest and shortest QT intervals ,QTCd: maximum QTc interval - minimum QTc interval, Tpe interval: measured from the peak of the T wave (highest point) to the end of the T wave, Tped: maximum Tpe interval - minimum Tpe interval.

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Table VI: Electrocardiographic parameters before and after intervention for TIBC categorization in children with IDA

	TIBC<440					TIBC>=440				
After-Before	Negative Ranks	Positive Ranks	Ties	z	p	Negative Ranks	Positive Ranks	Ties	z	p
TIBC	11	0	0	-2.938	0.003	34	0	0	-5.088	<0.001
PWAVE	11	0	0	-2.938	0.003	32	2	0	-5.038	<0.001
P dispersion	11	0	0	-2.934	0.003	34	0	0	-5.087	<0.001
QTC	11	0	0	-2.937	0.003	33	0	1	-5.022	<0.001
QTcd	11	0	0	-2.936	0.003	34	0	0	-5.088	<0.001
Tpe	11	0	0	-2.94	0.003	34	0	0	-5.09	<0.001
Tped	11	0	0	-2.934	0.003	29	5	0	-4.368	<0.001
TPe/QTC	11	0	0	-2.934	0.003	29	5	0	-4.368	<0.001

Total Iron Binding Capacity, P-wave: duration from the beginning to the end of the P-wave , P wave d: maximum P-wave duration- minimum P-wave duration, QT interval: started from the onset of the Q wave to the end of the T wave, QTc: was calculated using Bazett's formula ,QTd: Difference between the longest and shortest QT intervals ,QTCd: maximum QTc interval - minimum QTc interval, Tpe interval: measured from the peak of the T wave (highest point) to the end of the T wave, Tped: maximum Tpe interval - minimum Tpe interval.

Discussion

The study aimed to assess the impact of iron therapy on ECG parameters in children with IDA. The analysis included children aged 5 to 18 years, with a mean age of 11.47 ± 4.00 years. The gender distribution was nearly balanced, with 23 girls (51.1%) and 22 boys (48.9%). The results showed a general increase in blood measures, except for TIBC, alongside a decrease in ECG parameters following treatment.

Significant improvements were observed across all metrics, including ferritin, serum iron, TIBC, and ECG parameters, with a statistical significance of $p < 0.001$. These changes were consistent in both Hb groups, but children with Hb levels below 9 showed faster recovery.

Similar trends were noted in other subgroups, particularly in children with ferritin levels ≤ 10, those with serum iron levels between 21 and 28, and in the group with TIBC ≥ 440, suggesting that the therapy's positive impact was more pronounced in these groups.

IDA has a significant impact on the cardiovascular system, particularly on ECG parameters, due to the essential role iron plays in erythropoiesis and oxygen transport (13). Iron supplementation therapy improves these ECG parameters by addressing the root cause of anemia and enhancing Hb and ferritin levels through several physiological mechanisms(14). Iron is a crucial component of Hb, the protein responsible for transporting oxygen in red blood cells. In IDA, the reduction in iron availability leads to decreased Hb levels, impairing oxygen delivery to tissues, including the heart.

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This oxygen deficiency can cause disruptions in cardiac function and electrical stability, manifesting as ECG abnormalities such as prolonged QT intervals and T wave changes. By increasing Hb levels, iron supplementation restores oxygen delivery, leading to improved myocardial function and greater electrophysiological stability(15).

Ferritin, which stores and releases iron as needed, is typically low in IDA, indicating depleted iron reserves. This exacerbates anemia and its effects on the cardiovascular system. Iron supplementation increases ferritin levels, ensuring that there is a sufficient iron reserve for Hb synthesis and other essential metabolic processes. Higher ferritin levels are associated with improved cardiac function and normalization of ECG abnormalities, including ST segment and T wave issues(16).

In IDA, TIBC is often elevated due to increased transferrin levels and reduced iron saturation. Iron therapy lowers TIBC by replenishing iron stores, leading to more efficient iron transport and utilization. This reduction in TIBC is linked to the normalization of ECG parameters, as improved iron availability enhances cardiac muscle function and stability(17) in which support the cardiac functions and electrical stability(18). Research, including studies like Kwon et al. (19), has demonstrated that baseline Hb levels play a pivotal role in the normalization of ECG parameters, often leading to a quicker reduction in the risk of arrhythmias and other cardiac abnormalities during the treatment of IDA. These findings in the same line with present finding that suggests children with lower baseline Hb levels tend to show more severe ECG abnormalities but may also experience faster improvements as their Hb increases with iron therapy (20). Moreover, the degree of Hb elevation is closely associated with the rate at which ECG parameters normalize. A substantial rise in Hb can lead to quicker corrections in the QT interval and T wave changes and other ECG parameters, highlighting the critical need for monitoring Hb levels throughout iron supplementation to evaluate the effectiveness of treatment and its positive impact on cardiac health (9). These findings, along with present study's results, confirm that iron deficiency even in the absence of other underlying health conditions can significantly affect cardiac electrophysiology. This underscores the importance of screening for and managing iron levels to prevent cardiac complications in IDA patients. Additionally, a unique aspect of the present study is its demonstration that higher pre-treatment Hb levels can accelerate the improvement of ECG parameters following ferrous sulfate treatment.

Iron supplementation increases ferritin levels, replenishing iron stores and enabling the production of adequate Hb. As Hb levels improve, the blood's oxygen-carrying capacity is enhanced, ensuring adequate oxygen delivery to myocardial tissues. This restoration of oxygen supply helps alleviate hypoxic stress on cardiac cells, leading to the normalization of ECG parameters, such as the QT interval and T wave morphology (9, 21).

An article examined the efficacy of ferrous sulfate (FS) and ferrous gluconate (FG) in IDA in toddlers aged 6-24 months. In a randomized clinical trial, 120 healthy toddlers received FS or FG (2 mg /kg / day) for six months. Blood tests showed no baseline differences, but post-supplementation results revealed significant improvements in Hb (Hb) and ferritin levels in both groups. The FG group achieved higher Hb (12.11 g/dL) and ferritin levels than the FS group (11.85 g/dL), with statistical significance. FG was more effective, supporting its use for IDA prevention in young children (22).

Findikli et al. (20) found that baseline ferritin levels play a critical role in

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determining how quickly ECG parameters improve following iron therapy. Children with lower baseline ferritin levels often exhibit more pronounced ECG abnormalities but tend to experience faster improvements as ferritin levels increase. The rate of ferritin elevation is directly linked to the normalization of ECG parameters, as rapid replenishment of iron stores helps correct hypoxia-induced cardiac dysfunction.

This leads to quicker improvements in abnormalities like prolonged QT intervals and abnormal T waves. Consequently, monitoring ferritin levels during iron supplementation is crucial for assessing the therapy's effectiveness and its impact on cardiac health (22).

These findings align with the current study's observation that negative ranks were higher in the Ferritin ≤ 10 group across all ECG parameters, indicating a more pronounced improvement in this group compared to children with Ferritin > 10. This suggests that lower initial ferritin levels may prompt more rapid ECG improvements during treatment. This comparison in the case of serum iron, highlights that the Negative Ranks are consistently higher in the 21 ≤ Iron serum ≤ 28 group for all ECG parameters, suggesting a more pronounced change in the negative direction in this group compared to the 15 ≤ Iron serum ≤ 20 group. Serum iron measures the amount of circulating iron bound to transferrin, a protein that transports iron in the blood. Low serum iron levels reflect insufficient iron availability for critical physiological functions. Iron supplementation restores serum iron levels, ensuring adequate iron for Hb synthesis and other cellular processes. This improvement supports cardiac muscle function and reduces ECG abnormalities. Studies have shown that increased serum iron levels are associated with better ECG outcomes, including normalization of the QT interval and improved heart rate variability (23).

The findings of this study emphasize the critical role of baseline serum iron levels in determining the speed of response to iron supplementation therapy. Higher baseline serum iron levels are associated with improved availability of iron for immediate utilization in Hb synthesis and other physiological functions. This results in a more rapid correction of anemia and faster improvements in ECG parameters. Conversely, severely low baseline serum iron levels necessitate a longer duration of supplementation to replenish iron stores, delaying noticeable cardiac benefits. Children with higher baseline serum iron levels demonstrated quicker normalization of ECG abnormalities, which can be attributed to the efficient correction of iron deficiency, enhanced oxygen delivery, and improved cardiac function. Specifically, for ECG parameters such as TIBC, PWAVE, P dispersion, QTcd, and Tpe, the Negative Ranks were significantly higher in the TIBC ≥ 440 group compared to the TIBC < 440 group. For QTc, a marked difference in Negative Ranks was observed, while for Tped and Tp-e/QTc ratio, the differences were smaller but remained statistically significant.

These comparisons highlight consistently higher negative ranks in the TIBC ≥ 440 group across all ECG parameters, suggesting more pronounced negative changes in this group relative to the TIBC < 440 group. TIBC, which reflects the blood's capacity to bind iron with transferrin, is typically elevated in IDA due to increased transferrin production as a compensatory mechanism in response to iron deficiency (24). These findings further underscore the importance of baseline hematological status in predicting therapeutic outcomes in IDA.

High TIBC indicates a lack of available iron for physiological needs. Iron supplementation reduces TIBC by

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increasing the amount of iron available for binding, thereby lowering transferrin levels. This normalization of TIBC reflects improved iron saturation and availability, which is critical for proper cardiac function and can lead to better ECG outcomes. Baseline TIBC values play a significant role in determining the speed of response to iron supplementation therapy (23).

High TIBC values indicate a high capacity but low availability of iron, necessitating a longer period of supplementation to rebuild iron stores and achieve noticeable cardiac benefits. As TIBC decreases with effective iron Treatment, iron becomes more readily available for Hb synthesis and other critical functions, leading to faster normalization of ECG parameters. Studies have indicated that children with lower initial TIBC values respond more quickly to iron supplementation, with rapid improvements in ECG abnormalities such as QT interval and ST segment changes. This rapid improvement is due to the more efficient correction of iron deficiency and the associated enhancement in oxygen delivery and cardiac function (23, 24).

Study limitation

The study may have a limited sample size and may not represent all demographic groups. Larger, more diverse populations would provide more generalizable results. Variations in measurement techniques for ECG parameters and iron levels could introduce inconsistencies in the data. Standardizing these methods would improve the reliability of the findings. Differences in baseline health conditions and co morbidities among participants were not fully accounted for, which could influence the results. Potential confounding factors, such as diet, medication use, and physical activity levels, were not controlled for, which could impact the study's findings. Controlling for these factors would improve the study's internal validity.

Conclusion

The present study demonstrated a significant correlation between iron deficiency anemia (IDA) and adverse changes in electrocardiogram (ECG) parameters. Specifically, groups with lower Hb, ferritin, and serum iron levels, as well as elevated total iron-binding capacity (TIBC), showed more pronounced ECG abnormalities. These findings indicate that IDA negatively affects cardiac function and electrical stability. Importantly, iron supplementation significantly improved ECG parameters by correcting anemia and restoring iron status. This underscores the critical importance of regular monitoring and management of iron levels to prevent and reduce cardiovascular complications associated with IDA. Routine screening for iron deficiency and anemia, particularly in high-risk populations, is essential for early intervention. Timely iron supplementation can prevent the progression of cardiac abnormalities and improve patient outcomes.

Data availability

The collected and analyzed data during the current study are available from the corresponding author on reasonable request.

Ethical Considerations

The study received approval from the Ethics Committee of Zahedan University of Medical Sciences, Iran (Ethics Code: IR.ZAUMS.REC.1399.373). It was also registered in the Iranian Registry of Clinical Trials under the number IRCT20250416065355N.

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of the most recent and relevant sources for this study.

Authors' Contributions

NMN played a central role in developing the study concept, designing the research, and overseeing the project. He also contributed to data interpretation and took the lead in drafting the manuscript. GMA assisted with data interpretation, conducted a comprehensive literature review, and was actively involved in manuscript revision. TB managed patient recruitment and care, ensuring that data were collected accurately and ethically. LT participated in data gathering and contributed to the literature review. SSM supported data collection, monitored patient follow-up, and helped prepare the manuscript for submission. AT carried out the statistical analyses, provided technical expertise, and offered critical feedback during manuscript drafting and revision. All authors reviewed and approved the final version of the manuscript prior to submission.

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Conflict of Interest

The authors affirm that they have no conflicts of interest related to this publication. The study was carried out with complete independence, free from any external influence. All processes, including data collection, analysis, and interpretation, were conducted objectively. Moreover, no financial, professional, or personal affiliations impacted the outcomes or conclusions presented herein.

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