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EFFECTS OF IRON REPLACEMENT IN IRON DEFICIENT CHRONIC HEART FAILURE PATIENTS IN SETTINGS OF GOVERNMENT SECTOR HOSPITALS OF KHYBER PAKHTUNKHWA

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ABSTRACT

Introduction: Heart Failure is a common problem and major cause of morbidity, mortality and impaired quality of life. Deficiency of iron is common in heart failure patients but the optimum diagnostic tests for detection of iron deficiency and treatment options to replace iron have not been fully characterized. This study was performed to determine whether intravenous iron therapy would improve the symptoms of iron deficient chronic heart failure patients.

Materials & Methods: This was a cross sectional descriptive study in which 96 patients with symptomatic cardiac failure NYHA class II and III were selected from selected tertiary care hospitals of Peshawar, KP, through convenience sampling. Serum ferritin, serum BNP, echocardiography and 6 Minutes' Walk tests were conducted on all patients, and 38 patients with iron deficiency (Serum Ferritin <100µg/ml) were identified. Intravenous iron was administered to the iron deficient patients weekly for 6 weeks and patients were reassessed through repeat investigations to determine the efficacy of intravenous iron administration in chronic heart failure patients.

Results: High compliance of patients with intravenous iron administration was observed (87%) with symptomatic, biochemical and physical evidence of improvement. After 6 weeks of treatment, reanalysis of these patients indicated significant improvements in Serum Ferritin levels ($p<0.001$), Serum BNP levels ($p=0.002$), Echocardiographic findings ($p=0.013$), 6 Minutes' Walk test ($p < 0.001$) and NYHA class shift in 76% of patients ($p<0.001$).

Conclusions: Parenteral iron administration is an effective modality in managing patients of NYHS class II and III cardiac failure patients.

Keywords: Heart Failure, Anemia, Iron Deficiency**,** Brain Natriuretic Peptide, Ferritin.

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INTRODUCTION

Iron has an important role in transport and storage of oxygen, metabolism of cardiac and skeletal muscles, synthesis and degradation of proteins, lipids and ribonucleic acid[1-7] and mitochondrial function.[8,9] Iron is essential for normal hematopoiesis, it is crucial for maintenance of cellular energy and extra-hematopoietic tissue metabolism.[1,2,4,5,7,8] Cells having high mitotic potential and increased energy demands are vulnerable to injury with decreased iron supply or abnormal utilization of iron.[1,2,5,7,8] In heart failure patients this is an important factor as in myocardium and peripheral tissues the abnormal energy generation and utilization contribute to heart failure pathophysiology.[10,11] Iron in higher concentration gets accumulated in cells and produces oxidative stress that initiate myocardial necrosis.[12] However at low level it initiates the enzyme nitric oxide synthetase activity and increased production of nitric oxide that promote cell survival through induction of signaling pathway.[12]

Iron deficiency associated with heart failure can be absolute or functional. The presumed mechanisms that are involved in absolute iron deficiency development, identified by depleted iron stores that are indicated through reduced levels of serum ferritin i.e <30mg/l, are GI bleeding due to antiplatelet drugs, decreased absorption due to bowel ischemia and or intestinal edema and inadequate nutrition.

In a study performed by de Silva et al. in 2006 on causes of anemia in heart failure patients, low iron or ferritin levels were found in about 43% of cardiac failure patients of which only 6% were having microcytosis.[13] Functional iron deficiency is inadequate iron supply, with abundant iron stores, due to iron locked in reticulo-endothelial cells and unavailability for metabolism of cells. In functional iron deficiency one mechanism is related to Hepcidin, a protein that regulates iron metabolism. In the initial stages of heart failure, Hepcidin levels are elevated but falls as the disease progresses; low Hepcidin level is an independent marker of worse prognosis.[14]

Ferroprotein is the only protein that exports intracellular iron; Hepcidin after binding to ferroprotein causes degradation of the later and prevent iron from re-entering the cells.[14] This leads to decreased absorption of iron in the duodenum and its retention in reticulo-endothelial cells, decreasing its concentration and availability in target tissues. A number of chronic disorders may be complicated by iron deficiency and it has recently been reported as a frequent cause of comorbidity in chronic heart failure patients regardless of ejection fraction.[15-18]

Table 1 provides a list of factors associated with anemia in patients of heart failure.

Table 1: Factors associated with anemia in patients with heart failure.

#	Factors associated with anemia
1.	Nutritional deficiency
2.	Intestinal malabsorption
3.	Hypovolemia with hemodilution
4.	Renal failure
5.	Hypothyroidism
6.	Bleeding
7.	Inflammation: increased serum cytokines (IL-6, TNF-α) and acute phase proteins (CRP)
8.	Treatment with ACE inhibitors

ACE= angiotensin-converting enzyme; CRP= C-reactive protein; IL-6= interleukin-6; TNF-α = tumor necrosis factor alpha.

In contrast to traditional views, the consequences of iron deficiency in heart failure patients are irrespective of anemia.[15-19] Thus iron replacement itself is considered as a striking therapeutic target in chronic heart failure; recently few clinical studies has been conducted to test this hypothesis.[20,21] Total body iron stores can be assessed through a number of clinical tests. Normal body iron ranges from 30-40mg/kg, 1.8gm is in red blood cells and 0.5-1.5gm is stored in liver parenchymal cells and reticulo-endothelial system.[22-24] Iron containing muscles protein and mitochondria contain less than 5% of total body iron. Daily iron loss from gastrointestinal mucosal cells sloughing is about 1-2mg/day that is balanced by an equal amount of absorption through gastrointestinal mucosal cells.[22,23,25,26]

Blood tests for routine evaluation of iron status include serum iron, total iron binding capacity, percent transferrin saturation, plasma ferritin, red blood cells protoporphyrin levels, sideroblast percent and erythrocytes morphology. In iron deficiency erythrocytes becomes microcytic hypochromic, iron binding capacity increases while other parameters go downwards (Figure 1).

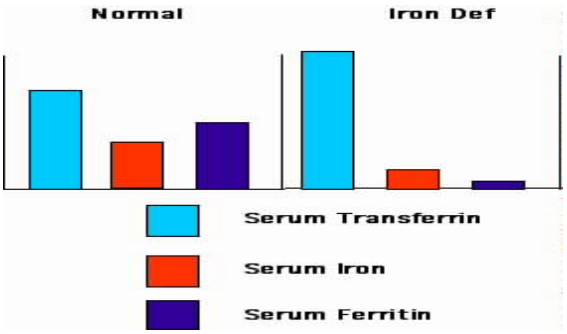

Figure 1: Graphical representation of biochemical changes during Iron Deficiency

In iron deficiency the clinical presentation is that of anemia, pica, stomatitis, glossitis, Plummer Vinson syndrome and restless leg syndrome.[23] Compromised thermoregulation, immunity and exercise tolerance have been attributed to low iron levels.[23] Chronic inflammation in cardiac failure patients may conceal the diagnosis of iron deficiency.[26-28] In chronic diseases iron retains within the macrophages, that leads to limited availability of iron for erythropoiesis.[29] The pro-inflammatory signaling molecules, tumor necrosis factor alpha, lipopolysaccharides and interferon gamma enhance the iron content of macrophages by reducing the expression of ferroprotein and increasing the expression of divalent metal transporter-1.[30] In anemia of chronic disease Hepcidin has also a major contribution by inhibiting the release of iron form macrophages through down regulation of ferroprotein.[31,32]

Several researchers have described the effects of iron replacement in patients of cardiac failure with or without anemia. Chronic inflammation in heart failure patients may camouflage the presence of iron deficiency anemia.[27,28,33] An important feature of chronic disease induced anemia is retention of iron within macrophages.[34]

Laboratory evidence of these molecular changes is variation in biomarkers consistent with a diagnosis of anemia of chronic disease. Weiss and Goodenough[29] proposed that in patients having inflammation and anemia, serum ferritin of <30ng/ml and transferrin saturation of <16% diagnosis of iron deficiency is likely. If transferrin saturation is low and serum ferritin is >100ng/ml the most likely diagnosis is anemia of chronic disease.

Table 2 provides the outcomes of different interventional studies of intravenous iron replacement for anemic cardiac failure patients.

Table 2: Studies on intravenous iron supplementation in patients with heart failure and anemia or iron deficiency.

Studies	Design	n	Clinical Context	Outcomes
Bolger et al.	Open, non-controlled; IV iron sucrose	16	Hb ≤12g/dl; NYHA II/III	↑Hb (1.4 g/dl); ↑QoL (MLHF); ↑6-min WT (44 m)
Usmanov et al.	Open, non-controlled; IV iron	32	Hb <11g/dl; NYHA III/IV	↑Hb (3---3.3 g/dl); ↓ LV remodeling
Comin-Colet et al.	Open; IV iron sucrose + EPO vs. no treatment	65	Hb ≤12g/dl; NYHA III/IV	↑Hb (13.5 vs. 11.3 g/dl); ↓ NT-proBNP; ↓ hospitalization (25.9% vs. 76.3%)
FERRIC-HF	Randomized, double-blind; IV iron sucrose vs. no treatment	35	FT<100 ng/ml or FT 100---300+TSAT<20%	↑VO_2 max 96 ml/min (p=0.08)
Toblli et al.	Randomized, double-blind; IV iron sucrose vs. placebo	40	Hb <12.5 g/dl; FT <100 ng/ml; TSAT <20%; LVEF ≤35%; NYHA II/III; LVEF ≤40%;	↓NT-proBNP; ↑QoL (MLHF); ↑6-min WT
FAIR-HF	Randomized, double-blind; ferric carboxymaltose vs. placebo	459	FT<100 ng/ml or FT 100---299+TSAT <20%; Hb 9.5---13.5 g/dl	↑PGA (50% vs. 28%): NYHA I/II; (47% vs. 30%)

EPO= erythropoietin; FT= ferritin; Hb= hemoglobin; IV= intravenous; LV= left ventricular; LVEF= left ventricular ejection fraction; MLHF= Minnesota Living with Heart Failure score; PGA= Patient Global Assessment score; QoL= quality of life; TSAT= transferrin saturation; VO_2 max= peak oxygen uptake; 6-min WT= 6-minute walk test.

MATERIALS & METHODS

This was a hospital based multi-center descriptive study with the purpose of improvement of cardiac functions through intravenous iron administration conducted at the Institute of Basic Medical Sciences (IBMS), Khyber Medical University. Data were collected through nonrandom convenience sampling from cardiac failure patients after obtaining written approval from cardiology departments of Lady Reading Hospital (LRH), Hayatabad Medical Complex (HMC) and Rehman Medical Institute (RMI), the three leading tertiary care hospitals of Peshawar, Khyber Pakhtunkhwa. Blood samples were analyzed in RMI laboratory.

Patients included in this study were those who were unable to perform 6 minutes' walk test, iron deficient with serum ferritin levels of less than 100µg/ml, and BNP levels more than 100pg/ml. Patients excluded were those having evidence of active GIT or genital tract bleeding, identified Vitamin B12 and Folic Acid deficiency, severe malnourished, pregnant patients and those who were non-consenting and non-compliant.

Data were collected through objectively designed Performa I and Performa II during patient's hospital visit. Performa I contained patient's bio data, history, physical examination and NYHA classification. In Performa II, six minutes' walk test findings and biochemical findings were recorded. After detailed history and clinical examination, blood samples were obtained for routine investigations and specific tests (serum Ferritin and Serum BNP) for diagnosis of iron deficiency and heart failure. Blood samples obtained in EDTA Vacutainer tubes were centrifuged to separate plasma. Plasma was transferred to Eppendorf tubes and frozen at –20°C until all samples are collected. When all samples were completed, then these Eppendorf tubes were thawed, vortexed, resuspended, and BNP levels were determined by using BNP-ELISA (Enzyme-Linked Immunosorbent Assay) kit.

Iron deficient subjects were started on I/V iron therapy Inj Venofer 200mg once a week for 6 weeks that is 2-4ml I/V diluted in 100ml 0.9% normal saline (NS) or 5% glucose. Six weeks after last infusion, repeat investigations were done for 6 minutes' walk test, serum ferritin and serum BNP to reassess these patients. Data were analyzed by SPSS version 15.0 for descriptive statistics.

RESULTS

Out of 38 iron deficient patients, 4 expired during their follow up visits and 5 were lost in follow up. Results are presented for the 29 patients with follow up.

Out of these 29, there were 13(44.8%) males and 16(55.2%) females with a mean age of 57.66±13.76 years (range 22-85 years, median age 58 years); 05(17.2%) patients were ≤49 years and 24(82.8%) patients were >49 years, indicating that iron deficiency is more common in heart failure patients of older age group (Table 3).

Table 3: Admission data of patients (n=29).

#	Variables	f	%
1.	**Gender**		
	Male	13	44.8
	Female	16	55.2
2.	**Age Groups (yrs)**		
	20-40	03	10.3
	41-60	14	48.3
	61-80	11	38.0
	>80	01	03.4
3.	**Marital Status**		
	Single	01	03.4
	Married	28	96.5
4.	**Hb Levels (g/dl)**		
	6.0-8.0	05	17.2
	8.1-10.0	10	34.5
	10.1-12.0	13	44.9
	12.1-14.0	01	03.4

Table 4 shows the baseline (pre-intervention) and post-intervention clinical and biochemical data of patients. A significant shift was seen in the NYHA classification with patients moving into better categories in the Post-Intervention period (p<0.001). However, the frequency distributions of other variables such as Left Ventricular Ejection Fraction, Six Minutes' Walk Test, Serum Ferritin, and Serum BNP did not change significantly despite improvements seen in the Post-Intervention figures.

Table 4: Pre- and Post-intervention clinical and biochemical data of patients (n=29).

#	Variables	Pre-Intervention f (%)	Post-Intervention f (%)	Total	p value
1.	**NHYA Class**				
	I	-	02 (06.9)	02	<0.001
	2	08 (27.6)	26 (89.7)	34	
	3	21 (72.4)	01 (03.4)	22	
2.	**Ejection Fraction (%)**				
	<25	04	03	07	0.76
	25-50	24	25	49	
	51-75	01	01	02	
3.	**Six Minutes' Walk Test (Meters)**				
	<100	09	02	11	0.079
	101-200	11	07	18	
	201-300	13	12	25	
	301-400	03	08	11	
	401-500	-	04	04	
4.	**Serum Ferritin (ng/ml)**				
	<100	29	02	31	0.33
	101-200	-	03	03	
	201-300	-	08	08	
	301-400	-	08	08	
	401-500	-	03	03	
	>500	-	05	05	
5.	**Serum BNP (pg/ml)**				
	<100	-	03	03	0.40
	101-200	02	02	04	
	201-300	-	01	01	
	301-400	04	01	05	
	401-500	-	04	04	
	>500	23	18	41	

Table 5 lists the mean values for the Pre-Intervention and Post-Intervention clinical and biochemical variables of these patients. All the variables showed significant improvements with p values ranging from 0.003 to <0.001.

Table 5: Mean values of clinical and biochemical data of patients (n=29).

#	Variables	Pre-Intervention (Mean ± SD)	Post-Intervention (Mean ± SD)	p value
1.	Ejection Fraction (%)	36.59 ± 11.54	37.97 ± 10.52	0.013
	Range	(16.0 – 73.0)	(20.0 – 73.0)	
2.	Six Minutes' Walk Test (Meters)	177.55 ± 104.45	288.48 ± 118.50	<0.001
	Range	(1.0 – 383.0)	(1.0 – 500)	
3.	Serum Ferritin (ng/ml)	59.62 ± 28.22	353.5 ± 189.75	<0.001
	Range	(5.21 – 96.86)	(27.0 – 864.0)	
4.	Serum BNP (pg/ml)	1915.54 ± 2038.82	665.03 ± 377.55	0.002
	Range	(158.20 – 9151.20)	(86.0 – 1306.20)	

DISCUSSION

Chronic heart failure (CHF) is increasingly perceived as a multi-system ailment which, further than the impairment of cardiac function, also disturbs the functional ability of other organs like kidneys and skeletal muscle. Heart failure leads to impaired functional ability, compromised QOL and intensified mortality rate. Iron deficiency (ID) is the most prevalent comorbidity in CHF that confers an independent worse prognosis.[35] Clinically very little data are available on the incidence of iron deficiency in HF patients in KP.

The present study shows that ID is equally affecting elderly CHF patients irrespective of gender. Patients with ID anemia present with impaired left ventricular ejection fraction, higher incidence of NYHA class III, decreased distance in six minutes' walk test compared with those without anemia.

Study results indicates that iron deficiency anemia (Hb<12.5mg/dl in males and <11.5mg/dl in females) is more common in elderly patients who are 49 years and above.

Iron therapy has profound effect on six minutes' walk test, NYHA class and BNP level.[19,36] Iron replacement therapy in ID CHF patients in NYHA class II or III with impaired left ventricular dysfunction showed a good safety profile, is well endured and satisfying in terms of symptoms irrespective of the presence of anemia.[19,36] An accurate assessment of iron status can be acquired in these patients by analyzing serum ferritin levels.

Serum ferritin has been used in this study to evaluate iron status, the choice has been made taking into consideration its readily availability and cost effectiveness. Serum ferritin of the participants showed significant improvement at post interventional stage.

Brain natriuretic peptide (BNP), a protein is released from the ventricles or lower chambers of the heart in response to changes in blood pressure that result with development of heart failure and is related to its severity.[37] In response to severity of heart failure, BNP levels in blood increase and the levels reduce with improvement in symptoms of heart failure.[37,38] In patients with heart failure even when condition is stable, BNP levels are raised as compared with normal functioning heart. BNP levels of all study participants are estimated at pre and post interventional stage for evaluation of cardiac activity.

Commonly used threshold levels for BNP is 100pg/ml. Specificity and sensitivity of more than 95% has been observed for BNP levels of 100pg/ml in comparing patient of CHF with patients without CHF.[37]

In present study there is remarkable reduction (65%) in BNP levels of patients that signifies the improvements in cardiac activity after I/V iron administration. Among all the parameters used in this study for evaluation of cardiac activity BNP seems to be an effective objective investigation as compared to NYHA classification, Echocardiography and six minutes' walk test.

Echocardiographic results were also significant after receiving intravenous iron therapy, the mean ejection fractions of pre and post interventional state showing a significant improvement ($p=0.013$). Echocardiography is a commonly prescribed investigation in diagnosing HF. It is a subjective and non-expensive test, the only drawback being inability to standardize. Thus I/V iron administration in ID patients with cardiac failure led to 4% improvement in ejection fraction.

Six minutes' walk test was performed in this study on participants for assessing exercise capacity. A significant improvement was noticed in post infusion test results ($p<0.001$).

Most important factors in assessment of clinical condition and prognosis of respiratory and cardiovascular diseases are exercise ability and patience.[35] Six minutes' walk test is reproducible and well-established assessment tool of functional ability that is subtle to changes in patients that report their symptoms. This has been used in different studies of HF to evaluate the effects of diverse intervention.[38,39] It is expected that targeting iron deficiency that affects oxygen transport and or utilization will improve patients exercise tolerance.

Remarkable improvement in six minutes' walk test distance was observed in almost all the subjects irrespective of anemia that again challenges the old view that link the adverse consequences of iron deficiency with anemia.

Six minutes' walk test showed a poor compliance as number of patients refused to perform or only performed it after detailed counseling.

Study outcomes revealed disagreement to the results obtained by other studies, pointing towards the effectiveness of other parameters used for the evaluation of improvements in cardiac activity after effective iron replacement as compared to six minutes' walk test.

Patient involved in current study characterize existing population of cardiac failure with adjusted medical treatment. The recruited patients were approximately identical numbers of patients in NYHA class II and III. The beneficial effects were observed irrespective of medical severity as demonstrated by no interaction among NYHA class, LVEF. That further widens the clinical applicability of result in this study.

In FAIR-HF study NYHA class and PGA were the primary end points for the evaluation of improvements in patient's cardiac activity.[39] Study results revealed that among the selected subjects for I/V iron administration a substantial number of patients had shown NYHA class shift after effective I/V iron administration.

In our study 39% of CHF patients had Iron Deficiency. Study results coincide with the results obtained from various international studies conducted on iron deficiency in CHF patients. Our study results support notion that the effects of iron replacement therapy on CHF patients may be independent of anemia. The observation is based on the fact that both the anemic as well as non-anemic patients showed significant symptomatic improvements after effective iron replacement. Iron replacement in ID and otherwise normal individuals irrespective of the presence of anemia was found to recover patience performance, maximum work and functional status of the individuals.

Confirm HF study showed that iron replacement in iron deficient heart failure patients resulted in marked improvements in functional capacity using six minutes' walk test.[40] These outcomes were constant in all groups comprising patients with and without anemia. Favorable effects of iron replacement through intravenous iron were established by improvements in patients QOL and functional position throughout the study.[37]

Data obtained from small clinical trial showed the advantage of intravenous iron among all oral iron on exercise tolerance in iron deficient anemic HF patients;[40] nevertheless analyzing just 18 patients it is far from being convincing. Large prospective randomized medical trials are needed in order to evaluate the efficacy of oral iron treatment in iron deficient CHF.

Assessing the effects of novel therapies in the settings of CHF it is expected that these would improve patient's symptoms and lessen the morbidity as well as mortality and prolong overall survival.[39] Recently it is observed that

there is marked reduction in mortality rate in CHF patients with parallel rise in hospitalization rate due to deteriorating of HF.[38] Hospitalizations due to worsening of HF are always associated with poor outcome and disability that constitute economic encumbrance for humanity thus there is an obvious necessity for its avoidance.[40] The current study was not planned to discourse the morbidity and mortality aspects of iron deficiency treatment using intravenous iron, but the obtained reports laid a sturdy ground for such studies to be executed further.

Most of studies conducted on ID in HF patient's ID has been corrected by using intravenous iron therapy with favorable outcomes but query rises, whether comparable outcomes will be obtained through oral iron administration or not. This intricate issue is still uninvestigated and unanswered. There are several reasons favoring usage of intravenous iron therapy and this seems to be the obvious therapeutic modality.

CONCLUSION

This study results demonstrated that intravenous iron replacement in NYHA I and NHYA II heart failure patients was well tolerated and it improved quality of life, functional status and exercise tolerance.

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