ROLE OF BRAIN NATRIURETIC PEPTIDE IN THE DIAGNOSIS AND MONITORING OF IRON DEFICIENT CHRONIC HEART FAILURE PATIENTS

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ABSTRACT

Objectives: To determine the efficacy of intravenous iron administration in iron deficient chronic heart failure patients and to determine the role of brain natreuretic peptide (BNP) in the diagnosis and monitoring of chronic heart failure patients.

Methodology: The current study was a prospective analytical study. A total of 96 patients with symptomatic chronic heart failure (CHF) were selected through convenient sampling method. These were divided in to several groups based upon findings of echocardiography, 06 minutes' walk test and serum BNP. It was found that 38 patients were iron deficient. Intravenous (I/V) iron sucrose was administered to iron deficient patients weekly for 6 weeks followed by reassessment; the compliance rate was 87%.

Results: Patients managed with I/V therapy showed significant improvement in all the clinical and biochemical parameters used in the study. New York Heart Association class shift was seen in 76% of patients.

Conclusions: iron deficient induced CHF is common in our population. Parenteral iron administration (iron sucrose) is an effective modality for managing such patients. Serial BNP levels can be used to monitor the response to IV iron.

Key Words: Heart Failure, Anemia, Iron Deficiency, Serum BNP

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INTRODUCTION

Congestive heart failure (CHF) is a remarkable medical challenge that is associated with high mortality, morbidity and economic burden[1]. Keeping in view the longevity of life seen in different parts of the developing and developed world; it is likely that the frequency of HF will continue to rise over the next 2-3 decades[2]. In the developing world, ID is likely to be much commoner due to lifestyle and dietary habits[3]. It would thus be a commoner contributory factor to HF, especially in the elderly. In spite of major advances in life saving managements, the ability to identify and optimally treat CHF is still restricted and not uniform in different segments of our healthcare systems.

There are different assessment tools for diagnosing CHF. Presently, the most common approach for diagnosing heart failure comprises of history and physical examination, echocardiography, electrocardiography and radionuclide ventriculography. None of these techniques are completely reliable, reproducible and or authentic for routine practice[4]. When there is suspicion of CHF, the most commonly advised investigation is echocardiogram for confirming the diagnosis and assessment of the severity. Echocardiography though a non-invasive technique thus preferred but is relatively expensive, not readily available, non-standardized and subjective test. There is extensive interest in recognizing brain natriuretic peptide (BNP) level in CHF patients. BNP and pro-BNP are currently used as marker for left

ventricular dysfunction and as tools for improving diagnostic and therapeutic monitoring[5]. These objective blood tests have been shown to be helpful in differentiating CHF from other causes of dyspnea, to have prognostic value, and helps in augmenting medical therapy. The level of BNP in the blood increases when heart failure symptoms worsen, and decreases when the heart failure condition is improving[6].

Clinically there is a growing interest in iron deficiency as a precipitating factor for heart failure patients. Deficiency of iron is one of the most common dietary deficiencies around the world that affects one third of the total population. A number of chronic disorders may be complicated by iron deficiency. In available studies, iron deficiency is linked with anemia and the difficulty in interpretation of iron deficiency is due to lack of prospectively validated definition of iron deficiency in heart failure patients[7,8]. Chronic anemia is coped well by normal heart without developing cardiac failure and left ventricular dysfunction, even in elderly people and those with low Hb levels[9].

There are a number of biochemical tests available for investigation and assessment of body iron stores. These may include the commonly available serum iron[10,11], total iron binding capacity (TIBC)[12], serum transferrin saturation[13] and serum ferritin. Serum protoporphyrin levels, plasma hepcidin and transferrin receptor saturation assay[14] are alternative tests. The latter tests are more expensive and not commonly available to most patients and are thus of limited clinical use in most countries. Among all the listed investigations, the most feasible and readily available investigation for iron status is serum ferritin level because of its cost effectiveness and ready availability in most health facilities around the globe[15-17].

Mechanisms involved in the development of iron deficiency in chronic heart failure patients are still to be fully understood[18-9] but iron deficiency may be due to impaired iron absorption, gastro-intestinal bleeding and decreased availability of iron from reticulo-endothelial cells[17]. Iron supplementation in patients with heart failure is well established. In a study a group of 16 iron deficient cardiac failure patients were given intravenous iron sucrose infusion for 5-17 days[20]. After a follow up period of three months, significant improvement in hemoglobin content, iron status and exercise tolerance was observed[20].

Determining the frequency of ID associated with CHF was the primary objective of this study. The cut-off point for iron deficiency in this study was considered as serum ferritin level below 100ng/dl[21]. An additional purpose of this study was to investigate the effectiveness of intravenous iron therapy in cardiac failure patients in our setting and to determine the best assessment tool among the echocardiography, six minutes' walk test, NYHA classification and BNP levels for diagnosis and monitoring CHF patients.

METHODOLOGY

This study was conducted in 2015. The study settings included Institute of Basic Medical Sciences of Khyber Medical University Peshawar, Department of Cardiology, Lady Reading Hospital Peshawar, Hayatabad Medical Complex Peshawar and Rehman Medical College Peshawar. Patients were selected through convenient sampling, after calculation of sample size through WHO approved formula. A total of 96 adult CHF patients were randomly selected and informed written consent was obtained; questionnaire (encompassing demographic and clinical details) was filled and blood sample collection followed. Their serum ferritin and BNP levels were sorted through chemilluminescence based assays employing 8K28 ARCHITECT BNP and 7K59 ARCHITECT ferritin kit on ARCHETECT System®.

The assessment was carried through serum BNP levels, 06 minutes-walk test on treadmill with the speed of 100 meter/minute, echo-cardiography and NYHA classification. Serum ferritin levels of all patients were performed to determine the number of iron deficient patients. Cut-off point for iron deficiency in this study was considered as serum ferritin level below100 ug/dl. Only 38 patients qualified the inclusion criteria (NYHA class II & III, ferritin levels <100ug/ml, BNP levels >100pg/ml). All of these were enrolled into the therapeutic trial. The patients were commenced on I/V iron therapy i.e. Inj iron sucrose 200mg once a week for 6 weeks that is 2-4ml I/V diluted in 100ml 0.9% N/S or 5% dextrose administered over two hours. Six weeks from last infusion all the investigations and clinical assessments were repeated. The data was analysed with IBM-SPSS® version 22. The study patients were divided into two age groups; group one <49 years and group two ≥49 years age.

RESULTS

A total of 96 cardiac failure patients were selected in which 38 were found to have ID as their serum ferritin was below 100 µg/l. Out of 96 patients, 48 were males and 48 were females. The minimum haemoglobin noticed was 6.0 g/dl and the maximum haemoglobin was 16.0 g/dl. Mean haemoglobin level of these 96 patients was 10.8 mg/dl. In these selected 38 iron deficient patients, 4 patients expired during their follow up visits and 5 patients lost in follow up. Table 1 describes the basic clinical and demographic characteristics of study patients.

Distance in kilometres from Peshawar was plotted against BNP levels at pre-interventional stage. Accord-

ingly, 06 patients were found in group 1 (area radius 20 km) having BNP levels of 0-1000 pg/dl. Of the rest, 07 patients were in group 2 (area radius >20 to 40 km), 10 in group 3 (area radius >40 to 60 km) and only one patient each in group 4 (area radius >60 to 80 km), group 5 (area radius >80 to 100) km and 2 patients in group 6 (area radius >100km). In distance group of 21-40 km, 10 patients in group 1 and 7 patients each in group 2 and 3 and 2 patient in group 4 and 3 in group 5 and 2 patients in group 6. In other group of 41-60 km number of patients were 5, 4, 1,1,0,0 in group 1, 2,3,4,5 and 6 respectively.

38 patients out of 96 were found iron deficient. When analysed through paired t test, pre-intervention mean ferritin level was 59.62 and post-intervention mean ferritin level was 353.48ug/dl with p-value of <0.001 (table 2). Intravenous iron administration increased serum ferritin level up to 492.8%. Compliance rate observed during this study was 87%. Mean BNP level in pre-interventional state was 1915.5pg/ml and the same calculated after intervention was 665.03pg/ml with the p-value of 0.002. Serum BNP level reduced to 63% in iron deficient patient who had received intravenous iron infusions. Mean ejection fraction in pre-interventional state was 36.58% an improvement was seen with a value of 37.96% in post-interventional echocardiography, p-value of 0.0013. Intravenous iron administration in iron deficient patients with cardiac failure leads to 4 % improvement in ejection fraction.

The mean distance covered by patients in pre-interventional state was 177.55 meter that was changed to 288.48 meter after post-intervention test with the p-value of <0.001. Intravenous iron administration in iron deficient cardiac failure patients produced 64% increase in 6 minutes' walk distance. Compliance observed was poor.

DISCUSSION

In this study 38 patients were found iron deficient. Haemoglobin level ranged from 6.0-16.0 (mean 10.8) g/dl. In this study 39% of chronic heart failure patients with NYHA class II or III symptoms, impaired left ventricular ejection fraction, serum BNP level more than 100 pg/ml had iron deficiency. Similar to the results of previously conducted studies[22], patients with iron deficiency anemia were mostly females with impaired left ventricular ejection fraction, higher incidence of NYHA class III, decreased distance in 6 minutes' walk test compared to those without anemia. Commonly used threshold levels for BNP is 100 pg/ml. Specificity of more than 95% and sensitivity of more than 95% has been observed for BNP levels of 100 pg/ml in comparing patient of CHF with patients without CHF [23,24].

Serum brain natriuretic peptide (BNP) levels in pre-interventional state were 1915.5 pg/ml and post- inter-

Table 1: Demographic data of study patients

Varibles		N (Number of Patients)	Mean Ferritin	Mean Hb g/dl	Mean BNP levels pg/ml	Lost in Follow Up
Gender	Male	48	258	11.5	1739.3	3
	Female	48	294	10.5	1880	2
Age	<49	24	385	11.3	2050.62	2
	≥49	72	340	10.8	1729.3	4
NYHA Class	1	Nil				
	2	34	405.2	10.9	1899.03	Nil
	3	62	205.5	10.8	1760.6	5
	4	Nil				

Table 2: Comparative analysis of pre and post values of serum ferritin, six minutes' walk test, ejection fraction and BNP levels

Variable	Average		Compliance	P-value	Remarks
	Pre	Post			
Serum Ferritin Levels	59.62	353.48	Good	<0.001	Significant
Serum BNP Levels	1915.5	665.03	Good	0.002	Significant
6 Minutes' Walk Test	177.55	288.48	Poor	<0.001	Significant
Left Ventricular Ejection Fraction	36.58	37.96	Average Good	0.013	Significant

vention were 665.03 pg/ml (p-value of 0.002), that is significantly indicating the effectiveness of intravenous iron administration in cardiac failure patients. Echocardiographic results were also significant after receiving intravenous iron therapy (p-value 0.013). Echocardiography is commonly prescribed investigation in diagnosing HF, it is a subjective test and non-expansive but the only drawback is that it is not a standardized test.

NYHA classification of all study patients was done in pre and post interventional stage and has shown significant results in terms of improvement in patients after iron therapy. 76% of patients were observed to shift from their class after iron therapy. This classification is also subjective, symptomatic and non- standardized. Intravenous iron therapy was preferred due to its increase availability and feasibility as oral iron therapy has poor compliance and reduce rate of absorption in gastrointestinal diseases.

According to results shown in table 1 the mean BNP levels in male patients were 1739.3 and in female patients were 1880 indicating CHF in severe intensity is more common in females as compared to male study patients. Mean BNP levels when compared within the two age groups that are below 49 years and 49 years and above it were high in age group of 49 years and above indicating CHF in 49 years and above age group are more severe in intensity. On the other hand when BNP levels of different NYHA class of study patients was determined as shown in table 1, BNP level of NYHA class 2 was higher as compared to class 3 indicating the flaw of NYHA classification.

Distance in kilometre from primary health unit was considered at pre-interventional stage as a mean to evaluate the impact of availability of resource and state of the patients, according to that largest number of patients were found in group 1 having BNP levels of 0-1000 pg/ml were in distance group of 1-70 km, 18 patients each in group 2 and 3 and only four patients in group 4, 5 and 6. Results indicate that there is reduction in the numbers of registered patients as the distance from the tertiary care hospitals increases. Patient from nearby location with distance of 1-70 kilometres have easy excess to hospitals as compared to distant areas that are more than 280 kilometres away. Due to lack of hospitals in nearby locations, cardiac patients fail to survive.

Iron therapy had profound effects on 6 minutes' walk test, NYHA class and BNP levels. Among the selected patients drug compliance was significant, iron replacement therapy in iron deficient chronic heart failure patients in NYHA class II or III with impaired left ventricular function showed a good safety profile and good tolerance and was rewarding in term of symptoms improvement, regardless of the presence of anemia. An accurate evaluation of iron status can be obtained in these patients by analyzing serum ferritin levels. Serum BNP levels in pre and post iron replacement therapy is a reliable marker in diagnosing and monitoring of CHF status in such patients. In European and Australian guidelines treatment with iron replacement is suggested in iron deficient patients[25,26]. Intravenous iron replacement in heart failure patients was well tolerated and it improved quality of life, functional status and exercise tolerance. Heart failure patients may benefit through correction of iron depletion, anemia or both.

CONCLUSION

ID induced HF is common in our population. Parenteral iron administration (iron sucrose) is an effective modality for managing such patients. Serial BNP levels can be used to monitor the response to IV iron.

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CONTRIBUTORS

NK conceived the idea, planned the study, and drafted the manuscript. MTM, HU, AG, ZAW, JA and AST helped acquisition of data and did statistical analysis. MHU supervised the study and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.