

EFFECT OF A REGIMEN OF OPTIMAL MEDICAL THERAPY ON BRAIN NATRIURETIC PEPTIDE (BNP) LEVELS IN HEART FAILURE IN THE PAKISTANI POPULATION

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Contribution

All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: To document the effect of optimal medical therapy (OMT) on BNP levels in heart failure in Pakistani population.

Methodology: In this Quasi experimental study, 75 consecutive stage C heart failure patients that had not been on OMT were included. These patients had been referred to AFIC-NIHD Heart Transplantation Department for assessment regarding heart transplantation. Initial assessments were carried out in hospital. Patients who were on OMT already were excluded. The prescription (carvedilol, lisinopril, spironolactone) was introduced as in patient as per pre defined protocol after clinical, imaging and lab evaluation. The patients were followed up in clinic and the dose escalation was done at regular intervals in out patients department. Clinical and lab variables were collected included BNP levels before starting treatment and 4 weeks after treatment.

Results : Males were 75% and females were 25%. Mean age was 38.69 ± 12.98 years (range 18-70 years). Mean Ejection fraction was 23.9% (range 15 – 34%). At one month clinical status of all patients improved except one. The patients had improved from NYHA class-III to NYHA class-II of dyspnoea. The mean baseline BNP level was 1331 pg/ mL, and the BNP level 4 weeks after the OMT trial was 951.9 pg/mL. This reduction was statistically significant ($p=0.016$).

Conclusion: OMT improves the BNP levels within a span of one month in patients with advanced systolic heart failure. This also correlated with the clinical improvement in the patients, and it was observed that BNP levels helped to monitor patients objectively and adjust OMT.

Key Words: Brain natriuretic peptide, Heart failure, Optimal medical therapy

INTRODUCTION

The systolic heart failure syndrome carries significant morbidity and mortality. Optimal medical therapy in the form of beta blockers, Angiotensin converting enzyme inhibitor (ACEIs) or Angiotensin receptor antagonist (ARBs), and aldosterone antagonists improve morbidity and mortality.¹ β -Blockers are now considered to be the most powerful tool available to add to standard regimens for the treatment of heart failure and to prevent or even reverse its downward course of progressive left ventricular remodeling, decreasing functional capacity, poor quality of life, and ultimately, death.² Cohn et al showed the survival benefit with enalapril, which emphasizes that vasodilator therapy should be included in the standard treatment for heart failure.³ BNP increase has a prognostic value to predict mortality after cardiac failure or myocardial infarction.⁴ Medical therapy for heart failure has been shown to have a positive effect on BNP levels, as demonstrated in the COMET trial carvedilol therapy has a positive effect on NT-pro BNP and mortality.⁵ Except for digoxin, all the drugs used to treat HF decrease serum levels of BNP.⁶

The objective of the study was to document the effect of optimal medical therapy on circulating Brain natriuretic peptide (BNP) levels in heart failure in the Pakistani population.

METHODOLOGY

In this Quasi experimental study we prospectively collected data on 75 consecutive stage C heart failure (defined as per the AHA/ ACC guidelines for the management of heart failure 2009)¹ patients who had been referred to AFIC-NIHD heart transplantation department for the management of advanced heart failure and assessment for the need of heart transplantation. Patients included were 18-70 years old, having systolic heart failure diagnosed by using the Framingham criteria supplemented by Echocardiography demonstrating an EF of <40% ; in stage C heart failure and not on optimal medical therapy (as defined below). A patient was said to be already on OMT if the following were prescribed: Angiotensin converting enzyme inhibitor or Angiotensin receptor antagonist, Beta blocker, aldosterone antagonist and with or without loop or thiazide diuretics on a need basis. Aspirin and/ or atorvastatin added where it was required as a primary or secondary preventive measure for ischemic heart disease. All these drugs were required to be prescribed and continued in target doses as shown by the large scale randomised controlled trials of heart failure.

Candidates for Cardiac resynchronization therapy (CRT) or those already on CRT and candidates for Coronary artery bypass graft surgery or percutaneous coronary intervention based on angiographic and myocardial viability studies were excluded from the study.

All previous documentations, referral letters, prescriptions were reviewed. To ensure that all previous drugs being taken were documented thoroughly (for which physician notes may not have been available) medicine purchase receipts (where available) were reviewed as well. To identify any other medication patients might have been taking (which did not appear on the prescriptions) patients were asked to identify common medicine packs.

The patients underwent a detailed clinical evaluation including history and physical examination by a cardiologist. The echocardiograms were repeated at our hospital to confirm diagnosis and standardize measures for the study. LV function on echocardiography (using Philips IE-33 system) was assessed using standard 2D measures and EF calculations along with modified Simpson's rule and calculation of stroke volume and stroke distance was done as well. This was supplemented by visual estimation of ejection fraction and assessment of regional wall motion abnormalities. Investigations performed included ECG, complete blood count, serum urea, creatinine, Na, K, bilirubin, ALT, alkaline phosphatase. BNP levels were performed at base line using AxSym chemistry analyser (Abbot).

Optimal medical therapy was instituted as per the following prescription:

1. Tab Lisinopril started at 2.5 mg once daily with dose doubling every one week as tolerated, target dose was 10 mg. (Reason for choosing lisinopril is elaborated in the discussion below)
 - a. Indications to deviate from this protocol were angioedema, deteriorating renal functions or hyperkalaemia.
2. Tablet Carvedilol 3.25 mg twice daily with dose doubling every one week as tolerated, target dose was 25 mg twice a day.
 - a. Indications to deviate from this protocol were 2nd or 3rd degree AV block, symptomatic bradycardia < 50/ min, or clinical worsening of heart failure.
3. Tablet Spironolactone 12.5 mg once daily with dose doubling every one week of therapy, target dose was 50 mg once a day.
 - a. Indications to deviate from this protocol were hyperkalaemia, and endocrine side effects.
4. Furosemide was given on a need basis depending upon the fluid status of the patient.

Patients were followed on a weekly basis as outpatients and clinical assessment was carried out in terms of BP, pulse, body weight, ECG, serum urea, creatinine, serum Na, K. Dose adjustments of the drugs were made on a weekly basis as outpatients. At 01 month after starting OMT BNP levels

Table 1: Percentile Distribution of BNP Before and After OMT

Percentiles	Baseline BNP	Repeat BNP after OMT
25	252.2000	159.8500
50	896.2000	461.0000
75	1926.8000	1071.4000

were repeated in outpatients.

The data was analysed using SPSS version 17.0. Non-parametric tests (Wilcoxon Signed Ranks test) were applied to look for statistical significance between the values. P-value ≤ 0.05 was taken for statistic significance.

RESULTS

The total study population comprised 75 patients. Males were 75% and females were 25%. Mean age was 38.69 ± 12.98 years (range 18-70 years). Mean Ejection fraction was 23.9%, (range 15 – 34%). At one month the clinical status of all patients had improved except one. The patients had improved from NYHA class-III to NYHA class-II of dyspnoea. There had been no emergency visits of these patients for acute cardiovascular de-compensation. There was no clinically discernible fluid overload in these patients. Target doses of all drugs were achieved in all the patients without any limiting adverse effects.

The mean BNP levels at baseline were 1331.0 ± 1309.8 pg/ml and at four weeks after OMT they fell to 951.9 ± 1047.1 pg/ml. Non-parametric tests for significance showed the difference between the values to be statistically significant ($p=0.016$). The distribution of BNP pre and post treatment in percentiles groups is shown in Table 1.

DISCUSSION

Evidence based OMT in heart failure reduces morbidity and mortality. This has been emphasized in all international practice guidelines.¹ Beta blockers, have been shown to improve symptoms reduce arrhythmic risk and mortality in multiple trials.⁸⁻¹⁰ The beta blockers which have shown mortality benefit in heart failure so far include carvedilol, bisoprolol, and metoprolol XL. Prescribing metoprolol tartrate for mortality reduction is not supported by evidence based guidelines; it's use was tested in the MDC study¹¹ which showed a beneficial effect for the combined end point of morbidity and mortality, primarily driven by the morbidity end point without a mortality benefit. ACE inhibitors have been shown to reduce mortality in major trials as well.¹²⁻¹⁵ In our study we chose Lisinopril because of its unique pharmacokinetics that makes it more manageable and easy to titrate. It is a class III ACEI which is not a pro drug, is water

soluble, is not metabolized in the liver, and is excreted unchanged by the kidneys.¹⁶

Similar benefits have been shown for Angiotensin receptor blockers¹⁵, and aldosterone antagonists (AA).¹⁷ While withdrawal of Digoxin from the treatment regimen causes clinical deterioration it has not been shown to confer any mortality benefit.¹⁸

Optimal medical therapy definitely leads to varying degrees of clinical improvement in different patient subsets. This creates the need for laboratory measures that can objectify the clinical improvement as well as supplementing the improvement in ejection fraction on echocardiography. Circulating serum BNP seems to be one such promising lab marker.

BNP is used for emergency department diagnosis of heart failure in patients with acute dyspnoea. Cut off values for diagnosis of heart failure have been defined in different studies.¹⁹ Circulating BNP levels have been shown to be of prognostic significance across all stages of heart failure.²⁰ There are observational data to suggest that decrease in BNP or NT-pro-BNP concentrations by $\geq 30\%$ from initial values may actually signal towards improved prognosis.²¹ This finding was also reported by another study.²² This fact has been utilised to gauge its utility in objectively following patients with heart failure in clinic with varying results in different studies^{4,23-25} with a rather equal divide between the ones supporting and refuting the need for BNP guided heart failure management in outpatients. Medical therapy for heart failure has been shown to have a positive effect on BNP levels.²⁶

In our study we sought to study the effects of optimal medical therapy on BNP levels in the indigenous population which has not been previously reported. In our study we found that there was a statistically significant reduction in BNP levels on a predesigned regimen based on beta-blocker (carvedilol), aldosterone antagonist (spironolactone) and ACE inhibitor (Lisinopril). This translated well into improvement of clinical status, and allowed us to objectively follow our patients and optimise medical therapy. With regards to the latter it was our observation that the change in BNP levels helped to provide positive feedback to both the physician and the patient, reinforcing their belief in OMT. This

enhanced physician prescription and achievement of target doses of OMT while improving compliance by the patient.

The study is limited by raising further questions of whether the reduction in BNP levels actually translates into reduction in long term mortality in our patients. This is likely to be answered by the long term follow up of these patients.

CONCLUSION

Optimal medical therapy improves the BNP levels within a span of one month in patients with advanced systolic heart failure. This also correlated with the clinical improvement in the patients, and helped to monitor patients objectively and adjust optimal medical therapy.

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