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Original Research Article.

A Study to Assess the Role of NT-proBNP as a Marker of Cardiac Mortality In Hemodialysis Patients

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ABSTRACT

Background: Increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are associated with cardiovascular mortality in hemodialysis patients. The present study was conducted to assess the role of NT-proBNP as a marker of cardiovascular mortality in hemodialysis patients.

Materials and Methods: NT-proBNP concentrations were measured in 50 prevalent hemodialysis patients to examine the risk of 90-days and 1-year mortality associated with baseline NT-pro BNP concentrations. Data was analyzed using standard descriptive statistics. Wilcoxon signed rank test and Welch two sample t-test were used in "R" commander statistical software.

Results: The NT –pro BNP values at the entry into the study of short term i.e.90 days follow up death group were significantly (p value = 0.002647) high when compared to remaining live dialysis participants (n = 40). But the difference in NT –pro BNP values at the entry into the study between death and live participants was not statistically significant (p value = 0.7785) in long term i.e.1 year follow up participants. The difference in serum sodium at the time of entry, is statistically significant (p = 0.03564), between live and dead groups at the end of short term follow up.

Conclusion: Elevated NT-proBNP concentrations were observed in end-stage renal disease (ESRD) patients on dialysis at the entry of study and these values were associated with cardiac mortality in them. NT –pro BNP acts as a newer marker for cardiovascular risk in dialysis patients of ESRD.

Keywords: NT-proBNP, Hemodialysis, Cardiovascular Events.

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INTRODUCTION

Brain natriuretic peptide (BNP) belongs to the family of natriuretic peptides, which plays a major role in the regulation of blood pressure and extracellular volume through stimulation of natriuresis.[1]

BNP is produced by the ventricular myocardium in response to increased myocardial wall stress.[2] ProBNP acts as a prohormone, a circulating protease, cleaves pro BNP into the N-terminal fragment (biologically inactive - NT-proBNP) and C-terminal fragment (biologically active - BNP).[3]

BNP is cleared via degradation by neutral endo peptidases (NEP) through receptor mediated clearance (by binding to the natriuretic peptide receptor type C), and a small amount by the kidneys. The NT- pro BNP is not cleared via receptor mediated mechanisms, leading some to suggest that it will be more sensitive to changes in renal function.[3,4] Traditional risk factors like, hypertension, obesity, and hyperlipidaemia have the limited ability in defining the cardiovascular risk in hemodialysis patients.[5]

Although, significant advancement has occurred in the diagnosis and management of cardiovascular diseases, patients on chronic hemodialysis are showing significantly higher cardiovascular morbidity and mortality compared with age matched counter parts not on dialysis.[6]

Current practice guidelines suggest that patients should be routinely evaluated for cardiovascular disease risk factors before initiating dialysis.[7] Thus there is a need of newer markers in assessing the cardiovascular mortality in hemodialysis patients.

MATERIALS AND METHODS

The study was carried out from May 2018 to November 2019. This prospective study selected 50 ESRD patients, who were under hemodialysis treatment in the department of nephrology, SVS Hospital, Mahabubnagar. Informed consent was obtained from all study participants and the study protocol was approved by the institutional ethics committee. Patients without any cardiac diseases and morbidities except hypertension before starting the dialysis were included in this study. ESRD patients who were going to get the hemodialysis first time were also excluded from this study. At the entry of the study the blood was collected under aseptic conditions and the sample was divided into plain vacutainer tube for serum, and K2EDTA vacutainer tube for whole blood. The serum was used for measuring creatinine, urea, electrolytes, alanine transaminase, aspartate transaminase, calcium, phosphorus, iron and calculate the eGFR by using the MDRD formula. The NT-pro BNP was measured by using the whole blood sample in time resolved fluorescence method (Radiometer AQT 90). Then the patients were followed up after 90 days of enrolment into the study and the mortality was recorded. 7 participants mortality was recorded because of cardiovascular events and other 3 because of other than cardiovascular accidents like suicide, these incidents were excluded from the study. The remaining live participants were followed after one year of enrolment and 10 cardiac deaths were recorded. Death was confirmed by records of dialysis unit, in the department of nephrology, SVS medical college, Mahabubnagar.

Statistical Analysis

Baseline characteristics of study population were compared between patients who died with cardiovascular events and those who survived using standard descriptive statistics. Wilcoxon signed rank test and Welch two sample t-test were used in "R" commander statistical software.

Table 1: Mean values of various parameters and Median value of NT-pro BNP at the entry of this study among live and dead subjects after 90 days follow up

PARAMETERS	Live group	Dead group	p - value
Number (n)	40	7	
Age in years	48.52	53.28	0.3481
Male	23	6	
Female	17	1	
Blood Urea (mg/dl)	103.42	123.57	0.3136
Serum Creatinine (mg/dl)	7.87	7.72	0.8779
Serum calcium (mg/dl)	7.83	8.05	0.4936
Serum Phosphorus (mg/dl)	4.31	4.80	0.2822
SERUM ELECTROLYTES			
Sodium (mmol/l)	139.47	135.57	0.03564
Potassium (mmol/l)	4.54	4.84	0.1143
Chloride (mmol/l)	102.42	103.57	0.5389
Ionic Calcium (mmol/l)	1.01	0.96	0.4457
Alanine Transaminase / ALT (U/L)	14.83	15.42	0.2941
Aspartate Transaminase /AST (U/L)	18.16	16.85	0.5374
Serum Iron (µg/dl)	57.25	42.00	0.0971
Estimated GFR (ml/min)	7.99	8.57	0.7293
NT- pro BNP (ng/l)	10,255	22,345	0.002647

RESULTS

At the end of 90 days /short term follow up

The difference in patients NT- pro BNP values at the time of entry into the study between live and dead at the end of 90 days follow up was statistically highly significant. This means that NT-pro BNP value acts as a predictive marker of mortality at short term follow up in dialysis patients.

The difference in serum sodium at the time of entry into this study is statistically significant between live and dead at the end of 90 days follow up. The remaining parameters of this study did not show any significance. The results obtained are summarized in table 1.

At the end of 1 year /long term follow up:

The difference in considered parameters at the time of entry into the study are not statistically significant at the end of one year follow up between live and dead groups. The results obtained are summarized in table 2. Total study population was divided into 3 groups based on eGFR range. Results summarized in table 3. Inverse relation was established between eGFR and NT-pro BNP values but the relation was statistically not significant.

Further, the same values of NT pro BNP at entry into this study were divided into 3 groups of eGFR with equal width, but still the relation was statistically not significant as shown in table 4.

Table 2: Mean values of various parameters and Median value of NT-pro BNP at the entry of this study between live and dead after 1year follow up

PARAMETERS	Live group	Dead group	p - value
Number (n)	30	10	
Age in years	48.73	47.90	0.8731
Male	17	6	
Female	13	4	
Blood Urea (mg/dl)	103.2	104.1	0.9442
Serum Creatinine (mg/dl)	8.07	7.27	0.3906
Serum Calcium (mg/dl)	7.89	7.64	0.434
Serum Phosphorus (mg/dl)	4.44	3.91	0.2177
SERUM ELECTROLYTES			
Sodium (mmol/l)	139.46	139.50	0.977
Potassium (mmol/l)	4.60	4.37	0.3012
Chloride (mmol/l)	102.43	102.40	0.9826
Ionic Calcium (mmol/l)	1.02	0.96	0.148
Alanine Transaminase / ALT (U/L)	14.88	14.70	1.0
Aspartate Transaminase /AST (U/L)	18.71	16.50	0.4674
Serum Iron (µg/dl)	52.83	70.50	0.2172
Estimated GFR (ml/min)	7.73	8.77	0.3171
NT- pro BNP (ng/l)	10,327	10,254.5	0.7785

Table 3: Mean values of NT-proBNP in patients with different eGFR ranges

Groups	eGFR range	NT –pro BNP (mean)	Members (n)	p- value
Group I	3.52 – 6.4	16317.69	15	0.6879
Group II	6.4 -9.07	15395.73	16	
Group III	9.07 -16.5	13998.75	16	

Table 4: Mean values of NT-proBNP in patients divided into eGFR with equal width

Groups	eGFR range	NT –pro BNP (mean)	Members (n)	p- value
Group I	3.51 – 7.85	16023.50	28	0.5619
Group II	7.85 – 12.2	14301.79	14	
Group III	12.2 – 16.5	13423.20	5	

DISCUSSION

In this study, we aimed to examine the correlation between blood levels of NT-proBNP concentrations and cardiovascular mortality in haemodialysis patients. Several studies have established NT pro BNP as a marker of cardiovascular risk in general population as well as in patients with kidney disease.[8-10] Our current study has shown significant positive correlation between NT-proBNP concentrations and cardiovascular mortality at short term follow up i.e. 90 days. The NT –pro BNP values at the entry of study of these short term death group were significantly high when compared to remaining live dialysis participants.

In addition, NT-proBNP has been shown as an indicator of asymptomatic cardiac organ damage in patients who eventually develop left ventricular hypertrophy, left arterial dilation, atrial fibrillation, and left ventricular systolic dysfunction.[11]

Increased intravascular volume, resulting either from heart dysfunction or renal failure, increases the secretion of BNP. Natriuretic peptides promote tubular natriuresis and diuresis. BNP promotes natriuresis by opposing the rennin-angiotensin-aldosterone system and increasing GFR.[12] BNP acts through the kidneys to reduce intravascular volume, thereby decreasing it's own stimulus for secretion. But in renal dysfunction this effect is decreased, requiring more BNP to achieve the same level of activity as in the normal kidneys. Thus, renal dysfunction and heart failure act synergistically in their ability to increase the secretion rates of BNP and NT-proBNP.

Also, decreased renal function reduces the clearance of BNP and NT-proBNP. Several investigators indicated that elevated BNP and NT-proBNP concentrations can result from renal failure.[13-15] Similar results are obtained in our study. We established this result by dividing total study population into 3 groups of eGFR with equal counts in each group as well as dividing into 3 groups of eGFR with equal width. Many investigators suggested that higher cut off points for BNP and NT-proBNP should be implied as the CKD stage advances.[16,17] Our results confirmed previous studies that NT-proBNP concentrations are progressively higher in patients with more advanced CKD, as decreased renal clearance raises BNP and NT-proBNP concentrations.

Moreover, our study shows that serum sodium levels can be used as a marker for mortality like NT –pro BNP in short term follow up of these hemodialysis patients. The difference in serum sodium at the time of entry into this study is statistically significant between live and dead subjects at the end of 90 days follow up.

CONCLUSION

These findings suggest that measurement of NT-pro BNP and serum sodium concentrations may help identify patients at highest risk for adverse cardiovascular outcomes, especially within the first three months of dialysis, independent of established markers of cardiovascular disease. Also the association of NT- proBNP with mortality suggests that serial NT- proBNP measurements may help in guiding the therapy in patients on chronic hemodialysis.

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