Original Article

Prediction of Cardiovascular Events in Patients with Chronic Kidney Disease by Serial B-Type Natriuretic Peptide Levels

Bidita Khandelwal[1], Dheeraj Khatri[2], Vijay Pratap Singh[3], Devraj Saha[4]

Background : Patients with CKD and ESRD are at a high risk for cardiovascular complications and it accounts for about 50% of mortality Echocardiography is recommended by current guidelines as a fundamental tool for profiling cardiovascular disease in these patients but operator skill, and lack of availability of this technique at point of care are barriers. A rapidly assayed biomarker like B-type natriuretic peptide (BNP) with advantages of ease, low cost, availability and objectivity in measurement could be ideal for cardiovascular profiling in ambulatory care settings. High levels of BNP are related to adverse outcomes but it is difficult to interpret one-time BNP measurement. It is likely that serial BNP levels maybe more informative.

Objectives : (a)To perform serial B-type natriuretic peptide (BNP) testing at point of care (at baseline, 3 and 6 months) in addition to standard clinical and echocardiographic assessment for cardiovascular status in patients with CKD. (b) To evaluate if change in BNP levels from baseline is associated with cardiovascular events (CVE) over a subsequent six-month period.

Materials and Methods : After approval of Institutional Ethics Committee, a prospective hospital based study was carried out in the Department of Medicine at Sikkim Manipal Institute of Medical Sciences, Sikkim Manipal University, Gangtok for a period of two years (01.11.2013 to 30.10.2015).Adults with CKD stage 3 or higher were included. Those with history of or presence of CV disease were excluded. Baseline demography, clinical assessment and point of care measurements were recorded. All patients were followed up at third and sixth month with clinical and echocardiographic assessmentfor cardiovascular outcomes and BNP measurement.

Results : Out of 150 patients, a purposive grouping of sample was done to study differences between BNP of patients with Cardiovascular events (CVE) and BNP of patients without CVE. After grouping, descriptive statistics was computed for mean, standard deviation (S.D) and confidence interval (C.I). Correlation between BNP and CVE was analyzed by linear regression. For one occurrence of CVE, BNP value of 1164 was critical which was statistically significant at 95% C.I. (836.3, 1491.7). Number of patients who had a CVE at 3rdand 6thmonths were 18(12%) and 9 (6%) respectively. Most important derivation of this study was that first CVE requires more rise ie. 1164.05 but later only 642.1 is enough to cause CVE.

Conclusion : Thus it is seen that CVE & BNP levels is highly co relatable with p (<0.05) and serial measurements are more informative.

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Key words **: BNP, CKD, CVD, ESRD.**

Chronic Kidney Disease (CKD) patients are at a high risk of cardiovascular complications due to increased incidence of cardiomyopathy, cardiac hypertrophy, heart failure and coronary artery diseases[1]. Estimates reveal that 50% of mortality in patients with CKD are attributed to cardiovascular causes[2]. Thus profiling and risk stratification for cardiovascular risk in these patients is essential so

[1]MD (Medicine), Professor, Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim 737102 and Corresponding Author

[2]MD (Medicine), Associate Professor, Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim 737102

[3]MPT (Physiotherapy), Associate Professor, Department of Physiotherapy, KMC Mangalore, Karnataka 575003

[4]PGT, 2nd Year, Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim 737102

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Editor's Comment :

- An important cause of mortality in Chronic Kidney disease is cardiovascular complications. In emergency settings, dyspnea due to heart failure can be distinguished from other causes by B type Natriuretic Peptide. The predictive value of this biomarker in CKD is not established. Adverse outcomes in CKD are associated with high levels of BNP but it is difficult to interpret one-time BNP measurement. Serial BNP levels maybe more informative.

as to identify those at a high risk and to upgrade therapeutic interventions. Echocardiography is recommended by current guidelines as a fundamental tool for this[3]. Lack of expertise and availability of echocardiography at point of care is a major barrier for its widespread use. Hence the need for arapidly assayed biomarker which is ideal for cardiovascular profiling in ambulatory care settings. In emergency settings, dyspnea due to heart failure can be distinguished from other causes by B type Natriuretic Peptide[4]. As it is technically easy to perform, economical and reliable, thus it is widely used for clinical evaluation of congestive heart failure. The predictive value of this biomarker in CKD is not established High levels of BNP are seen in patients with CKD and relation with adverse events have been documented. But it is difficult to interpret one-time BNP measurement in such patients. Serial measurements of BNP levels at various points maybe more informative. An increase from the baseline may be indicative of worsening of the CKD or of new onset cardiovascular events. This would guide the clinician to modify the treatment promptly and accordingly.

Aims and Objectives

A prospective hospital based study was carried out in the Department of Medicine Sikkim Manipal Institute of Medical Sciences, Sikkim over a period of two years (01.11.2013 to 30.10.2015) with the objectives

a) To perform point of care serial B-type natriuretic peptide testing (at baseline,3 and 6 months) along with standard clinical and echocardiographic evaluation for cardiovascular status in CKD patients

b) To evaluate if change in BNP levels from baseline is associated with cardiovascular events (CVE) over a subsequent six-month period.

After obtaining approval from Institutional Ethics Committee, patients satisfying the following inclusion and exclusion criteria were informed about the study, written informed consent was taken and were recruited in the study.

Materials and Methods

Inclusion Criteria :

1. Age more than 18 years
2. Known to have Chronic Kidney Disease stage III or higher based on reduced eGFR (below 60ml/min/1.73m^2 body surface area as determined by MDRD formula) which is either present for at least 3 months or more, or reduced eGFR in presence of bilateral small kidneys (longitudinal diameter less than 9cm) on ultrasonography, or patients with known ESRD on renal replacement therapy(hemodialysis or peritoneal dialysis)

Exclusion criteria :

1. Patients with a known past history of manifest acute myocardial infarction (as evidenced by clinical symptoms, suggestive ECG changes, and raised cardiac enzymes) or definite unstable angina (as evidenced by clinical symptoms and ECG changes at the time of episode).
2. Patients with atrial fibrillation, second or third degree heart blocks or valvular lesions present at baseline.
3. Critically ill patients who require ICU admission at first presentation for severe hypervolumia, hyperkalemia, uremic encephalopathy or uremic pericarditis.
4. Patients who normally reside outside Sikkim
5. Unconsenting patients

Procedure :

A baseline assessment was based on administration of a questionnaire, simple point-of-care measurements and cardiac assessment. Questionnaire was administered to collect demographic variables and history of renal and cardiac disease. Simple measurements examination, and Point-of-care testing for Glycosylated hemoglobin and BNP at baseline was done. Cardiac assessment at baseline included evaluation for clinical features of heart failure (using Framingham's criteria), electrocardiography (to look for any evidence of chamber hypertrophy, and asymptomatic ischemia, and bundle branch blocks). Assessment of Left ventricular size, left ventricular end diastolic & systolic function and presence of any valvular abnormality was performed and data recorded in a pretested structured proforma. Serial BNP assessment was done by Point-of-care Alere Heart check system at baseline, at 3 months and at 6months.

Follow up : All patients were followed up at three-

Table 1 — *Comparing the baseline variables of two groups (n=150)*

	Group I n=40	Group II n=110	ρ value
Age	52.8±18.2	47.1±12.4	>0.05
Sex M:F	25:15	56:54	Not significant
Ht. (cm)	160 ± 8.1	161 ± 6.8	Not significant
Wt. (Kgs)	58.5 ± 12.2	60.6 ± 12.8	Not significant
Cholesterol	173.1 ± 47.2	160.8 ± 46.6	Not significant
TG	122.0 ± 27.8	130.5 ± 44.4	Not significant
HDL	36.7 ± 6.9	37.7 ± 8.7	Not significant
LDL	123.3 ± 31.5	118.5 ± 29.4	Not significant
CRP	23.7 ± 23.9	27.1 ± 25.8	Not significant
HbA1c	5.6 ± 0.7	5.6 ± 0.68	Not significant
LVID	5.2 ± 0.89	5.2 ± 0.91	Not significant
LVEF	52.9 ± 8.2	55.1 ± 10.8	Not significant

month intervals at third and sixth months after enrolment. The follow up included clinical assessment for cardiovascular outcomes, BNP measurement and echocardiographic assessment at each visit.

Outcome : Cardiovascular event was defined as cardiovascular death, new- onset acute coronary syndrome, pulmonary edema, or an arrhythmia requiring hospitalization and was a composite outcome. This outcome was verified using clinical presentation, electrocardiography or echocardiographic assessment as recorded by treating physicians.

Sample size : Anticipating a 20% event rate over the one year follow up from the baseline, a sample size of 138 would be sufficient to detect a hazard ratio of 0.60 with 85% power at two-sided alpha level of 0.05 and based on this150 participants were recruited in this study.

Results

Out of total data collection of 150 patients, a purposive grouping of sample was done to study differences between BNP of 40 patients with Cardiovascular events (group I) and BNP of 110 patients without Cardiovascular events (group II). After grouping, descriptive statistics was computed for mean, standard deviation (S.D) and confidence interval (C.I).

Test of homogeneity of variances was done. Then analysis of variances was done to find whether or not differences of two groups of BNP were significant for CVE.

Mean BNP level of group I (i.e. CKD with CVE) at presentation was 1182. 1 ±121.4(BNP1) and of group II (i.e. CKD without CVE) was 440.4 ±367.4(BNP4). The mean BNP levels of group I at 3 months and 6 months follow up was 1003.0±831.6 (BNP2) and 1386.1±115.5 (BNP3) respectively. The mean BNP level of group II at 3 months & 6 months follow up was 462.8±413 (BNP5) and 606.1±589.7 (BNP6) respectively. The inference is at any point of contact, either at baseline, at 3 months or at 6 months, the mean BNP level in group I was more than double of the mean of group II ie, those without CVE (Table 2).

On comparing the mean changes from baseline to 3 months & 6 months between the two groups, it was seen that in group I there was a reduction of 179 from baseline to 3 months and an increase of 204 from baseline to 6 months. In group II, the mean BNP change from baseline to 3 months and to 6 months was an increase of 22 and 165 respectively. Comparison between the group in statistically and clinically highly significant (P = 0.000).Linear regression was chosen as statistical measure to analyse the correlation between dependent variable (BNP) which is continuous and independent variables (ie, Cardio vascular events at 3rd & 6th month) which is categorical in nature and the results are as shown in Table 3.

For one occurrence of CV event BNP value of 1164 was critical which was statistically significant at 95% C.I. (836.3, 1491.7). Number of patients who had a cardiovascular event at 3rd and 6th months were 18 (12%) and 9 (6%) respectively. Most important derivation of this study was that patients with rise in BNP may have CVE with rise of 642.1at a later date. That means first CVE requires more rise i.e. approximately 1164.05 but later rise of only 642.1 is enough to cause CVE Thus it is seen that CVE & BNP is highly co relatable with p (<0.05).

Discussion

BNP has established its role in diagnosis of heart failure. But in patients with CKD, where elevated levels of BNP & NT pro BNP are frequently encountered, the role of BNP is not yet fully understood. Interpreting a single BNP level at presentation maybe unreliable due to the pre existing elevated levels. However, serial measurements may provide more reliable information as a predictor of cardiovascular events[5]. 50% of

Table 2 — *Comparing the serial levels of BNP between the groups (n=150)*

Groups	BNP 1		BNP 2		BNP 3	
Group I(n=40)	Mean	C.I	Mean	C.I	Mean	C.I
	1182.1±121.4	793.6 to1570.5	1003.0±831.6	737.0 to1268.9	1386.1±115.5	1016.1 to 1755.7
Group II(n=110)	BNP 4		BNP 5		BNP 6	
	Mean	C.I	Mean	C.I	Mean	C.I
	440.4±367.4	322.8 to 557.5	462.8±413.0	330.6 to 594.3	606.1±589.7	417.5 to 794.7

Group I: CKD with Cardiovascular events, Group II: CKD without Cardiovascular events
BNP 1: baseline BNP of Group I, BNP 2: BNP at 3 months of Group I,BNP 3: BNP at 6 months of Group I,
BNP 4: baseline BNP of Group II, BNP 5: BNP at 3 months of Group II, BNP 6: BNP at 6 months of Group II
C.I: Confidence Interval

Table 3 — *Correlation between BNP and CVE*

	R	R^2	p	F (ANOVA)	Coefficient (y=a+bx)	C.I
CVE 3rd	0.500	0.250	0.000	49.283	y =507.5+1164.05 x	836.3 – 1491.7
CVE 6th	0.543	0.295	0.000	61.907	y =523.433+642.173x	480.8 – 803.4

CVE 3rd: Cardiovascular event at 3rd month, CVE 6th: Cardiovascular event at 6th month

asymptomatic CKD patients and almost all of ESRD patients who are on renal replacement therapy have elevated BNP levels[6] BNP cut point is influenced by GFR and as the GFR declines, the BNP cut point becomes higher. An upper limit of 200pg/ml for an estimated GFR of 60ml/min/1.73 m 2 has a high level of diagnostic utility with anarea under the ROC curve of 0.80 across all CKD groups.BNP levels are strongly associated with left ventricular (LV) hypertrophy and LV systolic dysfunctionas well as with renal dysfunction. Patients with CKD have high incidence of LV hypertrophy and LV systolic dysfunction but even it its absence, BNP levels were observed to be independently associated with GFR and 24 hrs urinary output. Studies have shown BNP to be a better predictor of renal function compared to LV systolic function. While comparing BNP levels with echocardiography in patients with CKD in CREED study sensitivity of 88% and a positive predictive value of 87% in diagnosing LV hypertrophy was observed however, the specificity was only50% and the negative predictive value was only 53 %[7].

D Logeart *et al*[8] had concluded that among serial BNP measurements, pre-discharge BNP remains a strong predictor of death or re admission as compared to common clinical variables, BNP change during hospital stay and echocardiographic findings.

It has been observed that despite difficulty in interpreting BNP levels for diagnosis of LV dysfunction, high BNP is related with poor prognosis. Various studies have shown that highest tertile of BNP or NT-Pro- BNP predicts mortalityand cardiovascular death and provides an early indicator of cardiovascular compromise before echo-cardiography. This study primarily aimed to evaluate if change in BNP levels is associated with Cardio Vascular events(CVE) and it was found that the rise in BNP levels had a statistically significant correlation with occurrence of CVE. Also the serial testing during the follow up showed that at a later stage a comparatively lower level maybe enough for a CVE.

Conclusion

Serial BNP levels maybe more informative of cardiovascular events in CKD. However, there areno definite guidelines which are available for interpretation ofserial levels and how much increaseover thebaseline should be considered as clinically meaningful. Further studies can be carried out to detect the importance of pre-discharge BNP levels in predicting re admission or mortality in CKD patients.

Limitations : The co-relation between the echocardiographic findings and BNP levels was not done. Echocardiography was used to assess the cardiovascular status only.

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