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Original Research Article

Point of care estimation of B type natriuretic peptide levels in pediatric patients as a marker of cardiac disease

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ABSTRACT

Background: Early recognition of heart disease in children can be challenging, because children often have a limited repertoire of presenting signs and symptoms. Primary purpose of our study was to compare the levels of BNP in cardiac and non-cardiac pediatric patients admitted in PICU.
Methods: The study was conducted prospectively on 45 patients admitted in PICU. The i-STAT POC device (Abbott, East Windsor, NJ) was used for BNP measurement. Patients aging 1 month to 12 years, were enrolled in three cohorts: 1) Cardiac cohort, consisting of patients presenting with features of heart failure, 2) non-cardiac patients admitted in PICU with respiratory distress, 3) Critically sick, non-cardiac patients (PELOD score >20) without respiratory distress.
Results: Mean BNP levels in cardiac cohort were 2273 (±1302) pg/ml, which were significantly higher than those observed in respiratory cohort (9655±1223 pg/ml) and other critical illness group (102±168). The area under the ROC curve for BNP was 0.956 and at a value of 837 pg/ml, BNP has a sensitivity of 93.3 and a specificity of 93% to correctly identify CHF in cardiac patients.
Conclusions: We concluded that BNP levels are significantly higher in cardiac patients and point of care BNP estimation can easily distinguish between cardiac and non-cardiac patients. We also found that though BNP is raised in respiratory illness as well, levels are not very high as compared to cardiac patients.

Keywords: Brain natriuretic peptide, Congestive heart failure, Critically sick children, Pneumonia, Point of care

INTRODUCTION

The recognition of heart disease in children can be challenging, because children often have a limited repertoire of presenting signs and symptoms. Early recognition of cardiac disease can significantly impact the physician's ability to provide appropriate treatment, make necessary interventions, and affect patient outcome. An accurate laboratory marker of cardiac disease for pediatric emergency medicine does not exist.

B type natriuretic peptide (BNP) is a cardiac hormone with diuretic, natriuretic, and vasodilator properties.[1] BNP is secreted mainly in the ventricles in response to volume expansion and pressure load.[2-5] Measurement of plasma B type natriuretic peptide concentrations is increasingly used to aid diagnosis, assess prognosis, and tailor treatment in adults with congestive heart failure.[6] Limited data are available on the predictive value of BNP in pediatric patients with cardiac dysfunction.

BNP levels vary with age especially in the pediatric group. Immediately after birth, BNP levels are elevated and then rapidly decrease after the first week of life.[7] Renal immaturity may also contribute to decreased clearance of the BNP during the first week of life. As a result, the BNP levels are significantly elevated in newborns and drop rapidly over the first two weeks of

life. Thereafter, the BNP concentrations appear to hold steady until 12 years of age without any differences in gender.[7]

Many children present to pediatric emergency in congestive heart failure (CHF), mimicking a respiratory illness, thereby making the diagnosis of CHF challenging. Even in children with sepsis, myocardial dysfunction and vasomotor dysfunction may manifest as either warm or cold shock. Quantifying the degree of myocardial dysfunction in such children can be difficult. This necessitates the need of a point of care test, which could be performed in pediatric emergency itself to distinguish cardiac illness not only from respiratory illness, but other critical illnesses as well, and thus saving the precious time, which may be used for the appropriate management of the underlying condition. Furthermore, it may help in assigning the severity of the heart failure and thus defining prognosis too.

There is lack of data on BNP levels in non-cardiac pediatric patients, and we could not find any study directly comparing point of care BNP levels in cardiac and non-cardiac patients admitted in PICU.

METHODS

The study was conducted prospectively on 45 patients admitted in PICU from April 2022 to September 2022. The research was approved by institutional ethical committee of University College of Medical Sciences, Delhi, India (IECHR-2022-54-1-R1, dated 23.08.2022). The study was consistent with Declaration of Helsinki and written informed consents were obtained from all the participants. Primary objective of our study was to compare the levels of BNP in cardiac and non-cardiac pediatric patients admitted in PICU.

Inclusion criteria

All patients between the ages of 1 month to 12 years, who were admitted in pediatric intensive care unit with features suggestive of heart failure (Tachycardia, hepatomegaly, raised jugular venous pressure or pedal edema), or respiratory distress or any critically illness (PELOD score >20) were considered eligible to be included in study.

Exclusion criteria

Patient receiving inotropic drugs (Dopamine, dobutamine, adrenaline, vasopressin etc.) at the time of enrollment and patients with known chronic kidney disease were excluded.

Out of all the eligible patients, 15 consecutive patients were enrolled in three cohorts: 1) Cardiac cohort, consisting of patients presenting with features of heart failure, 2) non-cardiac patients admitted in PICU with respiratory distress, 3) Critically sick non-cardiac patients (PELOD score >20) without respiratory distress.

For cardiac cohort, patients with known case of congenital or acquired heart diseases were enrolled. For non-cardiac cohort, patients with respiratory distress or those with PELOD score of >20 were included. Respiratory distress is defined as per WHO criteria, which includes presence of either fast breathing or chest indrawing or stridor at rest.[13]

A venous blood sample of 0.5 ml was withdrawn in EDTA vial for estimating BNP levels. The i-STAT POC device (Abbott, East Windsor, NJ) was used for BNP measurement. The i-STAT BNP test cartridge uses a two-site enzyme-linked immunosorbent assay (ELISA) method. Antibodies specific for BNP are located on an electrochemical sensor fabricated on a silicon chip.

Sample size

In a study done by An et al mean serum BNP levels in cardiac patients were found to be 141.55 (±75.99) pg/ml, while mean serum BNP levels in pneumonia group were 26.0 (±14.57) pg/ml.[14] Assuming similar values in our patient, with alpha error of 0.05, and power of 90%, sample size comes out to be 12. We enrolled 15 patients in each limb.

Statistical analysis

Demographic characteristics such as age and gender of the study and control groups were determined and comparison was made between the groups. The mean plasma BNP values in the three groups were determined and compared. IBM SPSS Statistics 22 for statistical analysis program was used for evaluation of the findings obtained in this study. The normal distribution of parameters was analyzed by using Shapiro-Wilk test. The Student's t-test was used for the comparison of normally distributed parameters between two groups, while Mann-Whitney U test was used for comparison of two groups with non-normal distribution parameters. ANOVA test was used to compare the normally distributed parameters between 3 groups.

RESULTS

Mean age of patients were 19 months, 15 months and 35 months in group I, II and III respectively. The anthropometric measurements and baseline blood investigations (total leucocyte count, platelet count, blood urea, serum creatinine) were comparable between the groups with no statistical significance (Table 1).

Mean BNP levels in group I were 2273 (±1302) pg/ml, which were significantly higher than those observed in group II (9655±1223 pg/ml) and group III (102±168) as shown in Table 2. We could not find any significant

correlation between the BNP levels and severity of illness as measured by PELOD score.

Table 1: Baseline characteristics.

	Group I (Mean±S.D) (n=15)	Group II (Mean±S.D) (n=15)	Group III (Mean±S.D) (n=15)	F	P value
Age (months)	19.07±34.65	15.73±11.50	35.13±34.02	1.94	0.15
Weight (kg)	7.53±5.34	7.22±2.55	10.39±5.53	2.09	0.13
Length (cm)	69.10±25.18	72.76±13.53	83.46±22.55	1.89	0.16
BMI	14.99±4.28	13.29±2.30	14.23±3.04	0.98	0.38
MUAC	12.41±1.68	12.94±1.12	12.8±0.91	0.40	0.67
Hb	10.2±2.3	9.8±1.6	9.8±2.6	0.17	0.83
TLC	11020±5695	13506±7652	13306±8719	0.55	0.57
Platelet count	5.41±1.96	3.19±1.67	2.78±1.24	1.01	0.37
Blood urea	46.87±45.03	29.87±11.18	38.40±18.25	1.30	0.28
Serum creatinine	0.7±0.13	0.6±0.23	0.57±0.32	0.80	0.45
pH	7.23±0.13	7.42±0.11	7.35±0.91	4.99	0.12

Table 2: Comparison of mean BNP levels between 3 groups.

	Group I (Mean±S.D) (n=15)	Group II (Mean±S.D) (n=15)	Group III (Mean±S.D) (n=15)	F	P value*
BNP (pg/ml)	2273±1302	655±1223	102±168	17.77	<0.001

*one way ANOVA test

Table 3: Post hoc analysis: multiple comparisons.

	Mean difference	Standard error	P value#
Group I - Group II	1618.26	378.54	<0.001
Group I - Group III	2171.60	378.54	<0.001
Group II - Group III	553.33	378.54	0.319

#Tukey HSD test

The post hoc analysis of comparing different groups with each other (Tukey honest significance test) revealed significant difference between group I and II, and group I and III. However, there was no statistically significant difference (P value = 0.319) in BNP levels in group II and III (Table 3).

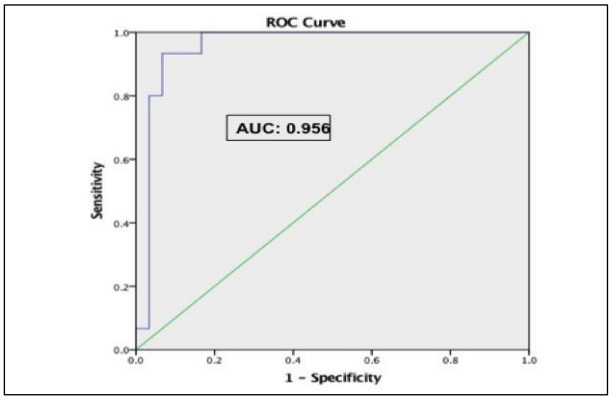

Figure 1: Receiver operating curve for BNP (AUC-0.956).

The area under the ROC curve for BNP was 0.956 and at a value of 837 pg/mL, BNP has a sensitivity of 93.3 and a specificity of 93% to correctly identify CHF in cardiac patients (Figure 1).

DISCUSSION

With advancement of diagnostic modalities and increased awareness among the practitioners there has been a steep rise in the incidence of heart disease, more so among the pediatric population. But still a proportion of children often land up straightaway in pediatric emergency in congestive heart failure (CHF) manifesting as respiratory distress, sometimes mimicking a respiratory illness thereby making the diagnosis of CHF challenging.

Robust data is available from past studies which supports the use of measurement of Brain natriuretic peptide (BNP) levels in adults to aid diagnosis, assess prognosis, and tailor treatment with CHF.[6] The normal BNP level in children is less than 100 pg/ml, slightly higher in neonates. However, patients who are diagnosed with heart disease usually have marked elevation of the BNP levels in the 2000-5000 pg/ml range upon admission.

Past studies on plasma BNP levels in the pediatric population have been conducted mainly on the differential diagnosis of pulmonary diseases and cardiac

diseases, monitoring the response of cardiac disease to treatment and prognosis.[8-10]

In our study, we found that BNP levels were significantly higher in patients with underlying cardiac condition, then those with respiratory or other critical illness. Evim et al reported that a plasma BNP level of 726 pg/ml was the threshold value for differential diagnosis of heart failure and pulmonary diseases.[10] Nevo et al showed that mean plasma N-terminal proBNP levels in children with non-cardiac diseases such as gastroenteritis, dehydration, and infectious diseases were significantly higher than in healthy children, but significantly lower than in children with cardiac diseases.[11] A systematic review by Costello et al. finds insufficient evidence to recommend the use of BNP in critically ill children.[12] Similarly, Charpentier et al reported that BNP levels were raised in adutls with severe sepsis or septic shock.[13] On the other hand, in a study by Domico et al, BNP levels were found to be significantly elevated in children with septic shock.[14]

In our study, we did not find any significant association between BNP levels and severity of illness as measured by PELOD score. A study by Auerbach et al has highlighted the association between elevated BNP levels and worse outcome. In children with moderately symptomatic CHF, BNP ≥140 pg/ml (hazard ratio, 3.7; 95% confidence interval, 1.62 to 8.4; P=0.002) and age >2 years (hazard ratio, 4.45; 95% confidence interval, 1.68 to 12.04; P=0.003) were independently associated with worse outcomes.[15] Similarly, Domico et al concluded that BNP levels at 12 hours of admission correlates directly with pediatric risk of mortality III (PRISM III) score.[14] A recent study conducted in Covid - 19 patients without previous history of heart failure found that NT-pro-BNP levels are independently linked with mortality in Covid-19 pneumonia without CHF.[16]

The study was limited by small sample size and heterogeneity of cases in the group III. The strength of study is the rapid measurement of BNP up on arrival in PICU. The study directly compares cardiac, respiratory and other critically sick children, which has not been done before.

CONCLUSION

We concluded that BNP levels are significantly higher in cardiac patients and point of care BNP estimation can easily distinguish between cardiac and non-cardiac patients. We also found that though BNP is raised in respiratory illness as well, levels are not very high as compared to cardiac patients. Role of BNP in critically sick children remains to be established and further studies are needed with primary focus of this group.

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