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Original Research Article

N-Terminal Pro B Type Natriuretic Peptide as Marker of Severity of Bronchiolitis in Children (3 months to 2 Years of Age)

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Abstract

Aim: The aim of the present study was to evaluate the utility of NT- pro BNP as a marker for assessing disease severity and outcome in previously healthy children between 3 months -2 years of age with bronchiolitis.

Methods: The proposed study was conducted in Paediatrics OPD, wards and emergency room of Vardhaman Mahavir Medical College and Safdarjung Hospital after clearance from Institutional ethics committee for the period of 18 months. 99 patients were included in the study.

Results: Approximately 50% of the enrolled children were between 6-12 months of age. Out of 99 children enrolled, 60.6% were males and 39.4% were females. Out of 73 children that were admitted, 7 had mild bronchiolitis, 33 had moderate bronchiolitis and 33 had severe bronchiolitis. All children with moderate bronchiolitis and 14/33(42.42%) with severe bronchiolitis had SpO2 90-94%. 19 children with severe bronchiolitis had SPO2 < 90%. Two children presented with shock and required admission in paediatric intensive care unit and mechanical ventilation. Median duration of hospital stay was 5 days (IQR 3-6 days, range 1-18 days). Corresponding values for children with mild, moderate and severe bronchiolitis were 1 day (IQR1-1 day, range 1-2 days), 3 days (IQR 3-4 days, range 1-7 days), 6 days (IQR 5-7 days, range 1-18 days) respectively and this difference between duration of stay in 3 severity groups was statistically significant (Kruskal Wallis test X2 = 44.5, p value < 0.001).

Conclusion: Our study showed that levels of NT pro BNP increased progressively with increasing severity of bronchiolitis. Median values in control, mild, moderate and severe groups of bronchiolitis were significantly different. There was a strong correlation between NT pro BNP levels and duration of hospital stay. Children hospitalised for > 7 days had significantly higher NT pro BNP levels as compared to those requiring hospitalization for ≤ 7 days.

Keywords: Acute bronchiolitis; Lung ultrasound; Echocardiography; NT-proBNP.

Introduction

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a low molecular weight peptide (8.5 kDa) expressed in the ventricular myocardium secondary to pressure and volume increases that has diuretic and natriuretic effects and is the most used biomarker for diagnosis and prognosis in heart failure.[1-3] There has been recent research interest in NT-proBNP as a reliable biomarker in several pediatric scenarios.[4] Increasing evidence supports the use of serum NT-proBNP levels as a potential biomarker of myocardial strain and disease severity for respiratory conditions, including acute bronchiolitis.[5-8] Serial monitoring of serum NTproBNP concentrations in these infants would require multiple blood sampling through venipuncture in an otherwise vulnerable population. NT-proBNP is a non-biologically active molecule with no active clearance mechanisms that is removed from plasma via passive excretion mainly by the kidney.[1,3,9,10]

The disease severity in bronchiolitis ranges from mild to severe. In majority of cases bronchiolitis is a self-limiting illness that can be managed on ambulatory basis. However, as per data from developed country 2-3% cases require hospitalization. Out of these, 2-6% requires paediatric intensive care unit admission (PICU) and advanced respiratory support [high flow nasal oxygen, continuous positive airway pressure (CPAP) support and invasive ventilation].[11-13] However, it has been seen that majority of children hospitalized for bronchiolitis lack these risk factors and nearly half of the children admitted to PICU with severe bronchiolitis are previously healthy.[13-14]

Treatment of bronchiolitis is mainly supportive. Therefore, early identification of infants at risk of developing severe disease is a major goal in order to provide more intensive monitoring and best management options at an appropriate time and appropriate level of healthcare faculty to potentially decrease the morbidity/ mortality. Though various clinical severity scores have been proposed, these have been used mainly in research studies to assess response to treatment and have not been validated for clinical decision making. Also ,clinical scores to assess clinical state have considerable inter-observer and intra-observer variability and they only assess clinical state at the time of evaluation and have no predictive value for subsequent illness course.[13-16] With bronchiolitis being a dynamic condition with significant temporal variability in symptoms and absence of a gold standard score to identify disease severity, as of now current guidelines recommend repeated clinical assessment and identification of risk factors for progression to severe disease as tools to make and tailor management decision.

So, efforts have been made to identify potential biological markers, or biomarkers that can predict disease severity and outcome at an early stage of disease to inform clinical decision making, especially in those children who do not have any risk factor for disease progression and are otherwise healthy.

N-terminal pro B type natriuretic peptide (NT-pro BNP) is one such biomarker that has been recently evaluated in assessment of bronchiolitis severity. Brain natriuretic peptide (BNP) is a 32 amino acid peptide released by cardio myocyte in response to ventricular wall stress due to pressure or volume overload that has natriuretic, diuretic and hypotensive effect. It is synthesized as pre pro hormone that is cleaved to form a pro hormone. This prohormone while getting released from the cells gets cleaved again into an active C terminal peptide and a biologically non-active N terminal peptide, the NT-pro BNP. NT-pro BNP levels are very high just after birth, decrease drastically in first week and

further decline during the first month of life and then remain steady with very gradual decline till 12 years of age.[17,18]

The aim of the present study was to evaluate the utility of NT- pro BNP as a marker for assessing disease severity and outcome in previously healthy children between 3 months -2 years of age with bronchiolitis.

Materials and Methods

The proposed study was conducted in Paediatrics OPD, wards and emergency room of Vardhaman Mahavir Medical College and Safdarjung Hospital after clearance from Institutional ethics committee for the period of 18 months. 99 patients were included in the study.

Inclusion Criteria: All children between 3 months -2 years of age diagnosed with bronchiolitis.

Exclusion Criteria: Children with underlying chronic lung disease, cardiac disease, immunodeficiency, neuromuscular disorder, chronic kidney disease, genetic disorder.

Detailed Methodology

The main components of the study were

1. All children between 3 months -2 years of age presenting to paediatric OPD, emergency room and diagnosed with bronchiolitis were eligible for enrollment.
2. Bronchiolitis was diagnosed clinically as first episode of wheezing in children < 2 year of age following a viral prodrome of 1-3 days. The viral prodrome is followed by cough, tachypnoea, or chest retractions or both and wheeze with or without crackles on auscultation. [11,19,20]
3. Eligible patients were enrolled into the study after taking informed consent from parents/guardian and ruling out exclusion criteria.
4. Patient were categorized into mild, moderate and severe bronchiolitis as per Indian Academy of paediatrics bronchiolitis severity classification.[21]
5. Measurement of NT-pro BNP level was done within 24 hours of admission in hospitalized children and on the day of assessment in children being treated on outpatient basis.
6. For NT-pro BNP measurement 1 ml whole blood sample was collected by venepuncture in EDTA vials and analysis was done by immunofluorescence assay of the Fincare NT-proBNP Rapid quantitative analyser. 75µl ml whole blood was used directly as a test sample. When testing could not be done immediately then serum sample was stored at 2-80C upto 1 day. Before testing sample was brought to room temperature.
7. Decision to admit and management of patients was done as per protocols of the treating unit under supervision of faculty.
8. Admitted patients were followed up to determine their clinical outcome (discharge/Leave Against Medical Advice / death).
9. Information regarding duration of hospitalization, need for ICU admission, need for ventilation (invasive / noninvasive) was recorded in predesigned proforma.
10. Patients treated on outpatient basis were telephonically contacted on day 3 and day 7 to determine their outcome (need for hospitalization or not).
11. Statistical analysis was applied as below.

Statistical Analysis:

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows:

1. Quantitative variables were compared using ANOVA/Kruskal Wallis Test (when the data sets were not normally distributed) between the groups.
2. Qualitative variables were compared using Chi-Square test /Fisher's exact test.
3. Pearson correlation coefficient/Spearman rank correlation coefficient were used to correlate BNP with hospital stay.
4. Independent t test/Mann Whitney test was used to associate BNP with requirement of ventilation, PICU admission, mortality, duration of stay >7 days and adverse clinical outcome as a whole.
5. Receiver operating characteristics was used to find out cut off point of BNP for predicting moderate and severe bronchiolitis and also to find out cut off point of BNP to predict adverse clinical outcome [need for PICU admission requirement of ventilation (invasive/non-invasive), mortality, duration of hospital stay >7 days].

A p value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using licensed Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Table 1: Age and gender distribution

Age groups	N%
<6 months	29
6-12 months	49
13-18 months	14
19-24 months	7
Gender	
Male	60
Female	49

Approximately 50% of the enrolled children were between 6-12 months of age. Out of 99 children enrolled, 60.6% were males and 39.4% were females.

Table 2: Distribution of admitted patients according to severity

Category	Admitted patients(n=73)	Not admitted (n=26)
Mild	7	26
Moderate	33	0
Severe	33	0

Out of 73 children that were admitted, 7 had mild bronchiolitis, 33 had moderate bronchiolitis and 33 had severe bronchiolitis.

Table 3: Oxygen Saturation (SpO_2) in Children with Mild, Moderate and Severe Bronchiolitis

Classification	SpO_2 (%)				Chi-Squared Test	
	>94%	90-94%	<90%	Total	$\chi 2$	P Value
Mild	33 (100%)	0 (0.0%)	0 (0.0%)	33 (33.3%)	139.021	<0.001
Moderate	0 (0.0%)	33 (70.2%)	0 (0.0%)	33 (33.3%)		
Severe	0 (0.0%)	14 (29.8%)	19 (100%)	33 (33.3%)		
Total	33 (100%)	47 (100%)	19 (100%)	99 (100%)		

At the time of admission all children with mild bronchiolitis had oxygen saturation (SpO_2) >94% with pulse oximetry. All children with moderate bronchiolitis and 14/33(42.42%) with severe bronchiolitis had SpO_2 90-94%. 19 children with severe bronchiolitis had SpO_2 < 90%.

Two children presented with shock and required admission in paediatric intensive care unit and mechanical ventilation.

Table 4: Duration of hospital stay in hospitalized children with mild, moderate and severe bronchiolitis

Duration Of Hospital Stay (Days)	Classification			Kruskal Wallis Test	
	Mild	Moderate	Severe	$\chi 2$	p value
Mean (SD)	1.14(0.38)	3.45 (1.33)	6.33(2.45)	44.510	<0.001
Median (IQR)	1 (1-1)	3 (3-4)	6 (5-7)		
Range	1 - 2	1 - 7	1 - 18		

Median duration of hospital stay was 5 days (IQR 3-6 days, range 1-18 days). Corresponding values for children with mild, moderate and severe bronchiolitis were 1 day (IQR1-1 day, range 1-2 days), 3 days (IQR 3-4 days, range 1-7 days), 6 days (IQR 5-7 days, range 1-18 days) respectively and this difference between duration of stay in 3 severity groups was statistically significant (Kruskal Wallis test X2 = 44.5, p value < 0.001). Thus, children with mild bronchiolitis who were admitted were discharged in 24 hours.

Table 5: NT-PRO-BNP Levels in Children in Mild, Moderate, Severe Bronchiolitis

NT-PRO-BNP	Classification				Kruskal Wallis Test	
	Control	Mild	Moderate	Severe	$\chi 2$	p value
Median (IQR)	107 (87-144)	522 (307.7-681.6)	2129 (1662-2591)	4730 (4150-6679)	87.042	<0.001
Range	22-170.6	170 – 1109	1092 - 2937	3416.7 - 29356		

Median (IQR) NT pro BNP levels in children with bronchiolitis at admission was 2129 pg/ml (IQR 699.5-4123.45 pg/ml, range170 - 29356). Children with mild, moderate and severe bronchiolitis had median (IQR) NT pro BNP levels of 522 pg/ml (307.7-681.6 pg/ml), 2129 pg/ml (1662-2591 pg/ml) and 4730 pg/ml (4150-6679 pg/ml). Children in control group had median NT-PRO-BNP level of 107 pg/ml (IQR 87-144, Range 22-170.6). Kruskal Wallis Test showed that NT pro BNP level significantly differed in control group and mild, moderate and severe bronchiolitis group ($\chi 2 = 87.042$, p = <0.001). Post-Hoc pairwise test for Kruskal-Wallis test showed that the values of NT pro BNP differed significantly between in control-mild, mild- moderate and mild-severe and moderate-severe group.

Table 6: comparison of NT PRO BNP Levels Between Children with Duration of Hospital Stay ≤7 Days and >

NT-PRO-BNP	Duration of Hospital Stay		Wilcoxon-Mann-Whitney U Test	
	≤7 Days	>7 Days	W	p value
Mean (SD)	3656.50 (3628.56)	18017.50 (16035.06)	7.000	0.032
Median (IQR)	2708(1711.4-4318.5)	18017.5(12348.25-23686.75)		
Range	253.5 - 28038	6679 - 29356		

Only 2 children required hospitalisation for > 7 days, rest 71 children were admitted for ≤ 7 days. Median NT pro BNP levels in children with duration of Hospital Stay ≤7 days were 2708 pg/ml (IQR 1711.4-4318.5, range 253.5 - 28038). However, the 2 children with duration of hospital Stay >7 days had significantly high NT pro BNP levels of 6679 pg/ml and 29356 pg/ml with median being 18017.5 pg/ml. Table 6

compares NT pro BNP levels between children with duration of hospital stay ≤7 days and > 7 days. Figure 7 shows Box whisker plot depicting distribution of NT pro BNP levels in the 2 groups.

Discussion

BNP and NT pro BNP have been extensively used as cardiac biomarkers. These have an established role in assessment of cardiac failure, have shown promising results for diagnosis of pulmonary artery hypertension and have also been used to distinguish between cardiac and respiratory cause of dyspnoea in children presenting to emergency room. Recently, there role as a marker of respiratory disease severity has been investigated with the premise that hypoxia, respiratory acidosis, inflammatory mediator release, direct endothelial damage and lung volume changes cause pulmonary vasoconstriction and subsequent pulmonary artery hypertension/increased right ventricular afterload and may lead to left ventricular myocardial dysfunction as well due to ventricular interdependence. Few studies have shown presence of increased pulmonary artery pressure/ myocardial dysfunction and its association with increased disease severity and outcome in previously healthy children with bronchiolitis. Few of these have also evaluated NT pro BNP as a marker of same. However, most of these studies have been done in children hospitalized with more severe disease and have not assessed NT pro BNP as a biomarker across the whole spectrum of disease severity. Also, no Indian studies are available in this contest. So, we did the study to assess role of NT pro BNP as a marker of disease severity of bronchiolitis in previously healthy children across the whole spectrum of disease severity.

We enrolled 99 children (33 each with mild, moderate and severe bronchiolitis) coming to out- patient department and emergency room, department of paediatrics VMMC and Safdarjung hospital. 33 healthy children (without any cardiac/ pulmonary/ chronic disease) attending OPD and undergoing blood sampling as part of their routine care were also enrolled as a control group for assessment of NT pro BNP levels. Median age of children with bronchiolitis was 8 months (IQR 5-12 months, age range 3 -24 months). and median duration of illness before presentation was 3 days (IQR 2-4 days). Majority of children with bronchiolitis (93%) were recruited from emergency room, probably because our hospital is a tertiary care hospital. Out of 99 children with bronchiolitis, 73 were admitted (7 with mild bronchiolitis, 33 with moderate bronchiolitis and 33 with severe bronchiolitis). Decision to admit the child was taken by treating unit based on various factor like distance of residence from hospital, parent's anxiousness and appearance of child. All children with mild bronchiolitis had oxygen saturation >94% while children with moderate bronchiolitis had spo2 between 90-94%. About 40% children with severe bronchiolitis had spo2 between 90-94% and remaining had spo2 <90%. Median duration of hospital stay was 5 days (IQR 3-6 days). This is conformity with previous studies that have shown median duration of hospital stay of 5-6 days.[22-24] Children having mild bronchiolitis were mostly discharged after 24 hours (median duration of hospital stay 1 day, IQR 1-1 day). Children with moderate and severe bronchiolitis had median duration of stay of 3 days (IQR 3-4 days) and 6 days (IQR 5-7 days) respectively. There was statistically significant difference in duration of stay of children in the 3 severity groups. Only 2 children had duration of hospital stay>7 days. 2 children presented with shock and required PICU admission and ventilation. 1 of these children expired. Thus, overall 3 children had adverse clinical outcome as defined by duration of hospital stay>7 days, need for PICU admission, ventilation and mortality. Median NT pro BNP levels at admission in control group was 107 pg/ml (IQR 87-144 pg/ml, range 22-170.6 pg/ml).

Median NT pro BNP levels in children with bronchiolitis was 2129 pg/ml (IQR 699.5-4123.45 pg/ml). Children with mild, moderate and severe bronchiolitis had median NT pro-BNP levels of 522pg/ml(IQR 307.7-681.6 pg/ml, range 170-1109), 2129 pg/ml(IQR 1662-2591 pg/ml, range 1092-2937) and 4730 pg /ml(IQR 4150-6679 pg/ml, range 3416.7-29356) respectively. There was statistically significant difference of NT pro BNP levels between control-mild, mild-moderate, mild-severe and moderate-severe groups. Study by Anıl M et al showed similar results using BNP as a biomarker of bronchiolitis disease severity, wherein, there was significant difference in BNP levels in children with mild, moderate and severe bronchiolitis.[25] Also, this result is similar to previous studies by Rodriguez-Gonzalez et al and that showed that hospitalized children with higher clinical severity score had higher value of NT pro BNP.[26,27] Our study also found a strong correlation between NT pro BNP levels and duration of hospital stay (spearman correlation coefficient 0.8, p value <0.001) with NT pro BNP levels increasing by 1057.10 pg/ml for every 1 day increase in duration of hospital stay. Also, children with duration of hospital stay >7 days had significantly higher NT pro BNP levels compared those with duration of hospital stay ≤ 7 days (18017.5 pg/ml vs 2708 pg/ml).

Number of children having predefined adverse clinical outcomes as defined by duration of stay >7 days, requiring PICU admission, need for ventilation or mortality was small in our study with only 2 children requiring PICU admission/ ventilation, 2 children having duration of stay >7 days and 3 children having overall composite adverse outcome. However, these children had significantly higher NT pro BNP level. These results share similarities with studies by Rodriguez-Gonzalez[26], Kes G[28], Anil Met al[25] wherein levels of NT pro BNP/ BNP have been found to be higher in children with more severe course of disease and outcome in the form of need for advance respiratory support, PICU admission, ventilation, prolonged duration of hospitalization and duration of oxygen requirement.

Study by Murat A et al[25], that is the only study evaluating BNP as a biomarker across the whole spectrum of bronchiolitis disease severity and included children with mild, moderate and severe bronchiolitis, showed result similar to our study. In this study, authors showed significantly different BNP levels between control and mild, moderate, severe bronchiolitis group. Also, BNP level correlation with duration of hospitalisation. Very few children in this study required PICU admission (n=3), mechanical ventilator (n=2) and these children had higher BNP levels.[25]

To conclude our study, evaluated NT Pro BNP levels at admission and across whole spectrum of bronchiolitis disease severity showed significantly different NT Pro BNP levels between control group and children with bronchiolitis. Also, there was significant difference in NT Pro BNP levels in children with mild, moderate and severe bronchiolitis and NT Pro BNP levels correlated with duration of hospital stay. Though very few children had duration of stay > 7 days, requirement of PICU admission, ventilation and only one child expired, these children had significantly higher NT Pro BNP levels. Thus, NT Pro BNP levels done at admission-time of evaluation can be used to predict bronchiolitis disease severity so as for institute management at an appropriate level of health facility. More studies are required to establish cut off value of NT Pro BNP levels to aid decision making.

Conclusion

Our study showed that levels of NT pro BNP increased progressively with increasing severity of bronchiolitis. Median values in control, mild, moderate and severe groups of bronchiolitis were

significantly different. There was a strong correlation between NT pro BNP levels and duration of hospital stay. Children hospitalised for > 7 days had significantly higher NT pro BNP levels as compared to those requiring hospitalization for ≤ 7 days. Significantly higher levels of NT pro BNP were also observed in children who needed PICU admission/ventilation and in the child who expired.

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