Original Article

Prognostic Value of Serum B-Type Natriuretic Peptide in Early Mortality and Morbidity of Children with Congenital Heart Disease after Open Heart Surgery

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Abstract

Background: *Brain type natriuretic peptide (BNP) is a cardiac hormone that is secreted mainly by the ventricles in response to volume expansion and pressure load. It can predict post-operative complications after heart surgery in adults. We sought to investigate the prognostic value of BNP in children after heart surgery.*

Methods: *We measured the BNP serum levels in 96 children with congenital heart diseases before, immediately after, and 12 hours after open heart surgery. We studied the ability of the post-operative BNP serum level variations to predict mortality and morbidity in children.*

Results: *In total, 96 patients, comprising 40 (41.7%) females and 56 (58.3%) males with a mean age of 4.1 years (range: 1 month to 17 years), with various congenital heart diseases were studied. The rise in the serum BNP level 12 hours post surgery was directly related to mortality before discharge from hospital (P value=0.004), congestive heart failure after surgery (P value<0.001) , patients' cyanosis (P value=0.045), duration of ICU stay (r=0.342, P value=0.004), and post-operative need for inotropic drugs (P value<0.001).*

Conclusion: *The rise in the BNP serum level 12 hours after heart surgery is a good marker for predicting mortality, morbidity, and early diagnosis of heart failure in children.*

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Keywords: *Heart defect, congenital • Cardiac surgical procedures • Natriuretic peptide, brain*

Introduction

Brain type natriuretic peptide (BNP) is a cardiac hormone with diuretic, natriuretic, and vasodilator properties that is secreted mainly by the ventricles in response to volume expansion and pressure load.[1] The measurement of plasma or serum BNP is increasingly used to aid diagnosis, assess prognosis, and conduct risk stratification in adults with congestive heart failure.[2-4] BNP is synthesized as pre-pro hormone, consisting of 108 amino acids; processing releases the biologically active 32-amino acid peptide and an amino-terminal fragment (NT-pro BNP).[5] The NT-pro BNP represents the N-terminal fragment of pro-BNP, the precursor of the biologically active BNP.[5] Unlike BNP, NT-pro BNP circulates at considerable concentrations in human plasma, is stable at room temperature for >24 hours, and can easily be detected and quantified by immunoassay.[6,7] These factors confer its potential as an additional tool in the assessment of ventricular systolic dysfunction.[6,7]

The plasma BNP level is useful in congenital heart

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diseases assessment, left and right ventricular dysfunction, congestive heart failure diagnosis and severity, and functional status in patients (adults and pediatrics) with pulmonary hypertension.[8-13] There is scarce information available concerning the plasma concentrations of BNP in children with congenital heart diseases after open heart surgery. The purpose of this study was to investigate the prognostic validity of serum BNP in pediatric patients with congenital heart diseases after surgery for an evaluation of mortality and morbidity.

Methods

Between October 2007 and July 2008, 96 patients, comprised of 56 (58.3%) males and 40 (41.7%) females with a mean±SD age of 4.1±3.5 years (range: 1 month to 17 years), were recruited into the study. These children had various congenital heart diseases (Table 1), which rendered them candidates for open heart surgery and they were, therefore, referred to Rajaei Heart Center (RHC: a tertiary medical center) from different parts of Iran. Our inclusion criteria were all children with any congenital heart diseases that were candidates for open heart surgery at RHC. Our exclusion criteria were any cases that did not have three blood samples for the BNP test (before, immediately after, and 12 hours after surgery).

All the cases underwent catheterization and angiography and echocardiography (with GE, Vivid 3) before surgery and serial echocardiography after surgery. NT-pro BNP was measured in all the cases before, immediately after, and 12 hours after surgery. Venous samples were collected into standard tubes and then serum NT-pro BNP was measured via the ELISA method, with Biomedica Slovakia s.r.o (SK-1204) Kits (with accuracy>95 %). The maximum duration from blood sample until test performance was 24 hours. The duration of ICU stay, ventilation time, pump time, aortic cross-clamp time, need for inotropic drugs after surgery, early mortality before discharge from hospital, and incidence of post-operative heart failure and low cardiac out put were determined. The study was approved by the RHC ethics committee with the permission of the children's parents.

Table 1. Frequency of various congenital heart diseases in the studied patients by type

Heart disease	Frequency	Percent
TOF	25	24
VSD	15.6	15
ASD	13.5	13
CAVSD	7.3	7
dTGA	7.3	7
PI	4.1	4
pulmonary atresia +VSD	3.1	3
DORV + PS	3.1	3
TAPVC	2.1	2
AS	2.1	2
ASD + VSD	2.1	2
ASD + PS	2.1	2
VSD + PS	2.1	2
Tricuspid atresia	2.1	2
Single ventricle + PS	2.1	2
MS	1.05	1
PS	1.05	1
AI	1.05	1
COA+ PDA	2.1	2
AP window	1.05	1
Total	100	96

TOF, Tetralogy of Fallot; VSD, Ventricular septal defect; ASD, Atrial septal defect; CAVSD, Complete atrioventricular septal defect; dTGA, d-Transposition of great arteries; PI, Pulmonary insufficiency; DORV, Double outlet right ventricle; TAPVC, Total anomalous pulmonary venous connection; AS, Aortic stenosis; MS, Mitral stenosis; PS, Pulmonary stenosis; AI, Aortic insufficiency; COA, Coarctation of aorta; PDA, Patent ductus arteriosus; AP, Aortopulmonary

Statistical Analysis

The data were classified by using mean±standard deviation for the interval and count (%) for the categorical variables. Because of the non-normal distribution of the BNP levels, a logarithmic transformation was performed to change the distribution to normal. The associations between the categorical and interval data were determined using Student's t-test. Simple linear regression models were utilized to investigate the associations between the interval data. The repeated measure analysis of variance (ANOVA) model was used to evaluate the changes in the BNP levels at different times. Statistical analysis was performed with SPSS 15 for Windows (SPSS Corporation, Chicago, Illinois).

Results

In total, 96 patients, consisting of 40 (41.7%) females and 56 (58.3%) males with a mean±SD age of 4±3.5 years (range: 1 month to 17 years), with various congenital heart diseases were studied. Table 1 shows the clinical diagnosis of our cases before surgery. The mean weight of our cases was 14.8 kg (SD±9.7). From all the cases, 61 (63.5%) cases did not have pulmonary hypertension and 35 (36.5%) cases had pulmonary hypertension (mean pulmonary arterial pressure above 25 mmHg at rest during catheterization and angiography). From all the cases, 49 (51%) patients were acyanotic and 47 (49%) cases were cyanotic (aortic O2 saturation <92%).

From the 96 patients, 46 (47.9%) cases had a low cardiac output or heart failure (ventricular ejection fraction <50% by echocardiographic examination and clinical diagnosis) after surgery. Fifty (52.1%) patients were treated with inotropic drugs (Epinephrine, Dopamine, Dobutamine, or Milrinone) after surgery for a low cardiac output, low arterial blood pressure, or low peripheral perfusion and oliguria. In our study, the mean duration of ICU stay was 6.6 (SD±11.5) days and the ventilation time after surgery was 18.7 (SD±18.6) hours.

All of these patients tolerated cardiac catheterization and angiography before surgery without any mortality or significant morbidity; however, from 96 cases with open heart surgery 7 (7.3%) patients died before discharge.

The mean serum BNP level before surgery was 48 (SD±68.8) fmol/ml; while immediately after surgery, this level rose to about 103 (SD±118.2) fmol/ml and after 12 hours, it reached 141 (SD±163.4) fmol/ml. These changes were statistically significant (P value=0.035). Significant differences existed between the BNP levels before surgery and the levels after surgery (both P values <0.001). The ANOVA model demonstrated significant differences in the serum BNP levels, between cyanotic and acyanotic patients, and between patients with pulmonary hypertension (PH+) and without pulmonary hypertension (PH-). The plasma BNP level in our patients before surgery directly correlated with pulmonary hypertension or right ventricular outflow tract obstruction (P value=0.02).

We considered the normal value of the BNP plasma level as less than 50 fmol/ml in accordance with other studies.[12,13] The BNP test had 51% sensitivity and 91.8% specificity in detecting PH. In this analysis, the ejection fraction of systemic ventricle in echocardiography before surgery in patients with or without PH was not significantly different. In our study, the BNP plasma levels did not correlate with the severity of PH (P value=0.69).

The marginal mean of serum BNP was 137 (SD±14.6) fmol/ml; 76 (SD±11.1) fmol/ml in the acyanotic patients (P value=0.02) and 129 (SD±15.5) in the PH+ and 84 (SD±10.3) in the PH- patients (P value=0.009). The interaction between cyanosis and BNP level was significant (P value=0.016). In other words, the trend in the BNP levels after surgery was different between the cyanotic and acyanotic patients (Figure 1).

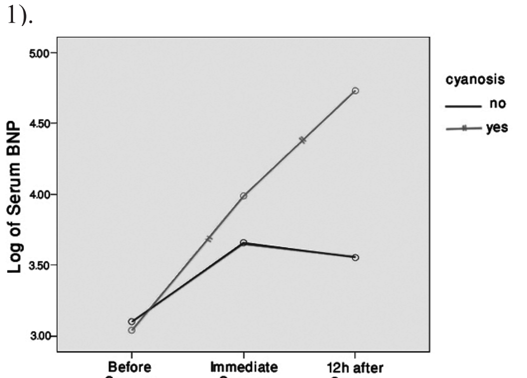

Figure 1. BNP levels after surgery were different in cyanotic and acyanotic patients

Associations between the change of BNP levels and other variables were as below.

At the baseline, no statistical relationships were observed between the BNP level (before surgery) and the other data. Tables 2 and 3 depict the associations between the rise in the BNP level 12 hours after surgery and the other study variables. The associations between this rise and the interval data were investigated using simple regression models.

The relationship between the BNP rise after 12 hours and the categorical data is shown in Table 2. It directly associated with heart failure or a low cardiac output (P value<0.001), cyanosis (P value=0.045), and need for inotropic drugs after surgery (P value<0.001) (Table 2).

Table 2. Comparison of the changes in serum BNP level between different subgroups of the study

	Mean (SD)	P value
Sex		0.068
Female (n=40)	99(175.1)	
Male (n=56)	90(150.1)	
Cyanosis		0.045
Yes (n=47)	146(179.1)	
No (n=49)	43(121.1)	
Heart failure		<0.001
Yes (n=46)	192(173.8)	
No (n=50)	3(68.2)	
Pulmonary hypertension		0.557
Yes (n=35)	89(167.2)	
No (n=61)	96(157.4)	
Need for inotropic agents		<0.001
Yes (n=50)	167(173.8)	
No (n=46)	13(93.4)	
Need for epinephrine		0.067
Yes (n=17)	164(184.8)	
No (n=79)	80(152.1)	

There were significant associations between the logarithm of the BNP rise, as a dependent variable, and age (β=-0.195, P value=0.002, R^2=0.136), weight (β=-0.078, P value=0.001, R^2=0.160), and duration of ICUstay (β=0.043, P value=0.004, R^2=0.117) as independent variables (Table3).

The rise in the BNP serum was not significantly associated with the duration of ventilation time after surgery. Also, the rise in the BNP serum level after open heart surgery was not associated with pump time or aortic cross-clamp time during cardiopulmonary bypass (Table 3).

We found that the rise in the serum BNP level 12 hours after surgery was directly associated with early mortality. The mean difference between the BNP levels before and 12 hours after surgery was 256 (SD±165.1) fmol/ml in the patients who died and 81 (SD±153.5) fmol/ml in the surviving patients (P value=0.004).

A logistic regression model was fitted to find the association between the difference of the BNP levels (after 12 hours post surgery) and mortality, adjusted for potential confounders such as age, weight, ICU stay time, and need for inotropic drugs. After adjustment, no significant association was observed between mortality and BNP changes.

Table 3. The parameters of simple regression models*

	Coefficient (β)±SE	P value	Correlation Coefficient (R)	R Square
Age (y)	-0.195±0.061	0.002	0.368	0.136
Weight (kg)	-0.078±0.022	0.001	0.400	0.160
Ejection fraction (%)	-0.016±0.020	0.445	0.094	0.009
Clamp time (min)	0.005±0.007	0.50	0.083	0.007
Pump time (min)	0.008±0.005	0.152	0.177	0.031
Duration of ICU stay (d)	0.043±0.015	0.004	0.342	0.117
Ventilation time (hr)	0.014±0.010	0.146	0.178	0.032

*Dependent variable, Logarithm (BNP level 12 hours after the surgery–BNP level before the surgery)

Discussion

There is an increasing interest in determining BNP and its N-terminal pro-peptides levels not only in patients with congestive heart failure but also in patients with congenital heart diseases. Recent studies have reported the usefulness of the NT-pro BNP levels in predominantly adult patients with various congenital heart diseases.[9,10,14] A few studies have been performed in children with congenital heart disease;[5] and a few studies have focused upon the BNP serum levels in healthy infants and children.[15] Other studies have documented the validity of the BNP serum levels in children with congenital heart diseases and heart failure.[10-13,16-20] In this study, a direct significant association between the BNP serum rise and post-operative low cardiac output or heart failure in children with congenital heart diseases was documented.

Jefferies JL et al.[17] reported that BNP was a strong serum marker in the early diagnosis of heart failure, which strongly chimes in with the findings of our study. We posit that the BNP serum level alone is not a good marker after open heart surgery in children for predicting mortality and morbidity, but the BNP serum level variations in any patient before and 12 hours after surgery are a very useful marker. This marker was associated positively and significantly with post-operative early mortality and morbidity (ICU stay duration, post-operative heart failure, and need for inotropic drugs) in children with congenital heart diseases. Early diagnosis of heart failure in children is very important for cardiologists immediately after heart surgery. Maher et al.[21] argued that BNP was a useful marker to aid in the urgent diagnosis of critical pediatric heart diseases in the acute care setting. We believe that the rise in the BNP serum level a few hours after surgery can be a useful and practical marker to aid in the early diagnosis of post-operative heart failure and to predict mortality and morbidity of children after heart surgery.

In another study, Maxime Cannesson et al.[22] showed that the BNP serum level could predict the adverse outcome in the post-operative period after arterial switch operation in neonates. In our study, the BNP serum level could predict mortality and morbidity of the children with various congenital heart diseases in the post-operative period. Although we did not compare our data with the BNP concentration in healthy children, we found that the BNP serum levels directly correlated with pulmonary artery or right ventricular pressures due to pressure overload of the right ventricle in children with congenital heart diseases.

Conclusion

The rise in the BNP serum level is a good marker for predicting early mortality and morbidity (adverse outcome) in children with congenital heart diseases after open heart surgery. Also, the BNP serum level rise is a reliable marker for the early diagnosis of post-operative low cardiac output or heart failure. The BNP serum level is a good marker for detecting PH in children with congenital heart diseases. Therefore, we conclude that in children with congenital heart defects, the BNP serum levels do not directly reflect the extent of ventricular pressure or volume load or severity of PH, but reflect more likely the degree of the impairment of the ventricles due to the increased volume and pressure work.

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