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Plasma brain natriuretic peptide values after ventricular septal defect repair: a potential predictor of negative outcomes

Ventriküler septal defekt tamiri sonrası plazma beyin natriüretic peptid değerleri: Olumsuz sonuçların potansiyel öngördürücüsü

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ABSTRACT

Background: This study aims to investigate whether there is a linear relationship between clinical outcomes and plasma brain natriuretic peptide levels following ventricular septal defect repair.

Methods: A prospective cohort study was designed at the pediatric cardiac surgery clinic of our institution. This cross-sectional study included 20 patients (13 boys, 7 girls; mean age 9.2±4.3 months; range, 4 to 18 months) who underwent ventricular septal defect repair between February 2012 and September 2012. Blood samples were taken at baseline before surgery, followed by six sampling at different time points during the postoperative course.

Results: In-hospital mortality was 5%. The mean preoperative B-type natriuretic peptide levels were significantly correlated with the preoperative mean pulmonary artery pressure ($p<0.001$). The mean B-type natriuretic peptide levels showed a great postoperative variation (mean±SD: 980.05±1125.38). The preoperative B-type natriuretic peptide values were significantly correlated with postoperative values at each time point. The correlation between intra-individual B-type natriuretic peptide, the mean and increased inotrope scores, prolonged time to extubation, and prolonged intensive care unit stay was under the limit of significance ($p>0.05$), whereas intra-individual B-type natriuretic peptide standard deviation was correlated with longer times of intensive care unit stay ($p<0.003$).

Conclusion: High intra-individual variability in serial measurements of B-type natriuretic peptide may be potentially a predictor of adverse outcomes following ventricular septal repair.

Keywords: B-type natriuretic peptide; congenital heart defect; surgery.

ÖZ

Amaç: Bu çalışmada ventriküler septal defekt tamiri sonrası plazma beyin natriüretik peptid değerleri ile klinik sonuçlar arasında doğrusal bir ilişki olup olmadığı araştırıldı.

Çalışma planı: Hastanemiz çocuk kalp cerrahisi kliniğinde prospektif bir kohort çalışması planlandı. Bu kesitsel çalışmaya Şubat 2012 - Ekim 2012 tarihleri arasında ventriküler septal defekt tamiri uygulanan 20 hasta (13 erkek, 7 kız; ort. yaş 9.2±4.3 ay; dağılım 4-18 ay) alındı. Hastalardan cerrahi öncesinde başlangıçta ve cerrahi sonrası dönemde altı farklı zaman noktasında kan örneklemesi yapıldı.

Bulgular: Hastane mortalitesi 5% idi. Ortalama B-tip natriüretik peptid düzeylerinin cerrahi öncesi değeri, cerrahi öncesi pulmoner arter basıncı ile anlamlı bir ilişki gösteriyordu ($p<0.001$). Ortalama B-tip natriüretik peptid değerleri cerrahi sonrası oldukça geniş dağılım gösteriyordu (ort±SS: 980.05±1125.38). B-tip natriüretik peptid düzeylerinin cerrahi öncesi değeri, cerrahi sonrası herhangi bir zaman noktasındaki B-tip natriüretik peptid değerleri ile ilişki gösteriyordu. B-tip natriüretik peptid düzeylerinin bireyler içi ortalaması ile artan inotrop skoru, uzamış ekstübasyon zamanı ve yoğun bakımda kalış süresi arasındaki ilişki istatistik olarak anlamlı bulunmazken ($p>0.05$), bireyler içi dağılımın standart sapması daha uzun yoğun bakım kalış süresi ile ilişkili bulundu ($p<0.003$).

Sonuç: Ventriküler septal defekt tamiri sonrası, ardışık B-tip natriüretik peptid ölçümlerinin geniş birey içi dağılım göstermesi, olumsuz sonuçların muhtemel bir belirteci olabilir.

Anahtar sözcükler: B-tip natriüretik peptid; doğuştan kalp defekti; cerrahi.

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Since first being identified by Sudoh et al.[1] in 1988, B-type natriuretic peptides (BNPs) have increasingly gained importance as a diagnostic and prognostic biomarker of heart failure. The human BNP is a cardiac natriuretic peptide that contains 32 amino acids and is produced both in the brain and the cardiac tissues.[2] The synthesis and release of pro-BNPs from ventricular myocytes are mainly stimulated by increased ventricular end-diastolic pressure and transmural wall tension.[3]

There have been several reports that emphasized the need for a reliable biomarker for the postoperative course of infants who undergo cardiac surgery for congenital heart defects (CHDs),[4,5] and recent studies have reported promising results regarding the use of BNP for predicting poor outcomes.[6,7] However, it has also been shown that BNPs show great intraindividual and temporal variability, especially in intensive care unit (ICU) settings where the hemodynamic parameters are subject to the effects of multiple factors.[8]

The clinical relevance of BNP in patients who undergo ventricular septal defect (VSD) repair is unclear and whether BNP measurement can be used in the evaluation of children with CHD is still controversial.[9] Therefore, in this study, we sought to determine whether there is a linear correlation between the outcomes and intraindividual BNP variability in infants who underwent VSD repair.

PATIENTS AND METHODS

This cross-sectional study was approved by the institutional ethics board of the Kartal Koşuyolu Education and Research Hospital (12.12.2011/17929), and parental informed consent was obtained for each patient to be included. In the beginning, we evaluated 53 patients who underwent cardiac surgery for isolated VSD repair at our facility between February 2012 and September 2012, and in the end, this prospective cohort study was composed of 20 infants (13 boys, 7 girls; mean age 9.2±4.3 months; range 4 to 18 months) with VSD (with or without associated defects) (mean weight 6,365±1,540 grams; range 4,300-9,000 grams). The surgery was performed in the cardiac ICU of our tertiary institution. The infants ranged in age from one to 24 months, and any who had poor renal or liver functions or who presented with severe respiratory insufficiency or major associated cardiac anomalies were excluded from the study. The diagnosis was primarily made via echocardiography. The preoperative diagnoses and associated abnormalities are given in Table 1.

All of the operations were performed by the same surgical team through a median sternotomy. Cardiopulmonary bypass (CPB) was established with dual selective caval cannulation using moderate hypothermia. After diastolic arrest, the myocardial protection was achieved with intermittent doses (every 20 minutes) of antegrade normothermic blood cardioplegia. All of the VSDs were approached via the right atrium, and all corrections were made using a Dacron patch that was attached with interrupted reinforced polyester sutures. In addition, ultrafiltration was performed routinely during rewarming. We then initiated inotropes, preferably dopamine, dobutamine, and epinephrine, to try and achieve adequate urine output per each patient's weight along with normal blood lactate levels.

The study data included the patients' demographics, echocardiographic variables, operative parameters, anesthetic parameters and postoperative courses, and the mean pulmonary artery pressure (mPAP), which was measured invasively before the CPB. The inotrope scores were calculated soon after weaning from the CPB at the 12^{th} and 24^{th} postoperative hours using a modification of the formula that had been previously described by Wernovsky et al.,[10] which is written as: dopamine (μgr/kg/min) + dobutamine (μgr/kg/min) + epinephrine (μgr/kg/min) + norepinephrine (μgr/kg/min) x 100. Furthermore, the mean central venous pressure (mCVP) values were recorded every six hours, and blood samples for the BNP measurements were taken at zero, five, 10, 24, 48, and 72 hours. Additionally, the lactate levels were measured simultaneously using a blood gas analyzer while the B-type natriuretic peptide measurements were made using the Siemens ADVIA Centaur® XP Immunoassay System (Siemens AG, Erlangen, Germany).

Statistical analysis

All statistical analyses were performed using the SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) software program. Visual histograms and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) were used for determining normal distribution, and continuous variables were defined using mean ± standard deviation (SD). The intraindividual descriptive variables for the serial measurements of the BNP levels (one preoperative and six postoperative at different time points) were represented as median ± interquartile ranges. Correlations among the variables were calculated using Spearman's rank correlation coefficient. A p value of less than 0.05 was considered to be statistically significant for the unit measurements, and a Bonferroni correction was used when multiple measurements

were carried out. The adequate sample size needed to achieve a 0.80 power level with a 0.008 probability of a type 1 error (for six paired measurements) and at least a 0.60 correlation [coefficient rho (ρ)] was estimated to be 25 patients.

RESULTS

The patients' baseline characteristics are given in Table 1. The distribution of the VSD subtypes was as follows: perimembranous in 13 patients (65%), subaortic in four (20%), and isolated muscular in three others (15%). In addition, patient number 9 had both perimembranous and muscular defects. The defect sizes measured 6.50 mm in diameter and had an interquartile range of 5.00-8.00 mm. Furthermore, large defects of >10 mm were present in three of the patients (15%). An atrial septal defect (ASD) was also present in two patients (10%), patent foramen ovale (PFO) occurred in three others (15%), and severe tricuspid regurgitation was seen in two patients (10%). In addition, patent ductus arteriosus (PDA) was present in 10 patients (50%), and a left persistent superior vena cava (SVC) was identified in one (5%). Pulmonary hypertension was defined as having an mPAP of >25 mmHg and was present in 13 patients (65%). In addition, the mean preoperative BNP levels were significantly correlated with the preoperative mPAP, but no other correlations were found among the other preoperative variables (Table 1).

The patient's operative data is given in Table 2. All but one out of the defects was closed with a Dacron patch, and in that patient (number 10), who had multiple defects, patch closure was used for the perimembranous defects and primary closure for the muscular defects. We also determined that the mean BNP values were significantly correlated with both increased aortic cross-clamp (ACC) and CPB times (Table 2) and that the preoperative BNP values were significantly correlated with the postoperative values obtained at each time point (r=873; p=0.001 at zero hours, r=0.642; p=0.02 at five hours, r=0.570; p=0.06 at 10 hours, r=0.605; p=0.05 at 24 hours, r=0.675; p=0.02 at 48 hours, and r=0.571; p=0.01 at 72 hours).

Table 1. Baseline characteristics, diagnosis, and correlation between the preoperative B-type natriuretic peptide values and clinical data

Patient	Diagnosis	BNP	Age (months)	mPAP	Weight (g)
1	Perimembranous VSD (>10 mm), PFO, and PDA	3.00	5.00	21.00	7000
2	Subaortic misaligned VSD, PLSVC, ASD, moderate TR, and PDA	396.00	6.00	37.00	5500
3	Muscular VSD (>10 mm) and PDA	122.00	4.00	52.00	4500
4	Perimembranous VSD (>10 mm) and PFO	1022.00	12.00	28.00	8500
5	Perimembranous outlet-type VSD (6 mm)	71.00	12.00	35.00	8000
6	Perimembranous VSD (>10 mm), PFO, and PDA	134.00	5.00	45.00	4000
7	Perimembranous outlet-type VSD (6 mm)	46.00	18.00	16.00	8000
8	Perimembranous VSD (7.5 mm) and PDA	26.00	14.00	35.00	6700
9	Perimembranous (5 mm) and muscular (8 mm) VSD	92.00	11.00	42.00	5000
10	Perimembranous VSD (6 mm), moderate TR, TSA, and PDA	60.00	5.00	26.00	6400
11	Perimembranous VSD (5 mm) and PDA	606.00	9.00	36.00	6300
12	Perimembranous outlet-type VSD (7/5 mm) and PDA	49.00	5.00	24.00	5600
13	Perimembranous VSD (5 mm)	88.00	15.00	22.00	8300
14	Perimembranous inlet-type VSD (>10 mm) and PDA	111.00	6.00	33.00	5300
15	Subaortic VSD (4 mm)	9.00	17.00	22.00	8300
16	Subaortic misaligned VSD (4.8 mm)	154.00	11.00	25.00	5600
17	Multiple muscular-type VSDs	62.00	7.00	44.00	6000
18	Muscular outlet-type VSD (7 mm),	3.00	7.00	10.00	9000
19	Subaortic misaligned VSD (>10 mm) and PDA.	115.00	9.00	28.00	4300
20	Perimembranous subpulmonic-type VSD and ASD	31.00	6.00	30.00	5000
	Mean	160.00	9.20	30.55	6365.00
	Standard deviation	248.53	4.32	10.45	1540.77
	Correlation coefficient between BNP values	-	-0.31	0.75	-0.51
	P value for correlation	-	0.10	0.001	0.02

BNP: B-type natriuretic peptide; mPAP: Mean pulmonary artery pressure; VSD: Ventricular septal defect; PFO: Patent foramen ovale; PDA: Patent ductus arteriosus; PLSVC: Persistent left superior vena cava; ASD: Atrial septal defect; TR: Tricuspid regurgitation; TSA: Tricuspid septal aneurysm;

In-hospital mortality occurred in only one patient (number 11) (5%). This patient underwent VSD patch closure, ASD closure, and PDA ligation and required high-dose inotropes during the cessation of CPB. The death occurred as a result of severe ventricular arrhythmia and low cardiac output syndrome (LCOS) on the postoperative second day. Moreover, the patient's BNP values were extremely high after the operation (4,700.00±600.00), and our attempts at managing the worsening hemodynamic parameters were not successful.

The BNP levels also showed great intraindividual variability. In order to emphasize the effect that this had, a correlation analysis of the postoperative outcomes was performed using both the mean intraindividual BNP levels and their SDs. A *p* value adjustment was then made for the repeated measurements using a Bonferroni correction, with the level of significance being determined as p<0.05/6=0.008. We also found that the mean intraindividual BNP and their SDs were correlated with longer ICU stays (Tables 3 and 4) and (Figures 1-3).

Additionally, when the probability of a type 1 error was set at 0.008, the intraindividual brain natriuretic peptide values of the 20 patients were positively associated with increased ICU stays (correlation coefficient =0.63), and they achieved 76% statistical power.

DISCUSSION

As suggested by the excessive deviations from the mean values obtained both before and after the operation, we found that the BNP values showed great variability among the patients who underwent VSD repair. The overall BNP values of the entire study group increased over time during the postoperative course, but they often took a downward turn after a certain time interval. This lack of a linear correlation among the average BNP values and surgical outcomes possibly suggests that the BNP levels cannot reliably predict the changes that evolve in individual patients, but they might partially reflect them to some extent. However, interindividual variability in BNP may potentially reflect the worsening status in patients who undergo VSD repair and require

Table 2. Operative details and correlation between the operative variables and mean postoperative B-type natriuretic peptide values

Patient	Operation	Mean post-operative BNP	°C	Cross-clamp minute	CPB minute
1	VSD patch closure + PDA ligation	284.33	28	50	70
2	VSD patch closure + PDA ligation	2479.67	30	70	100
3	VSD patch closure + PDA ligation	934.67	32	75	85
4	VSD patch closure	1105.83	32	40	58
5	VSD patch closure + septal obliteration	198.83	30	100	123
6	VSD patch closure + PDA ligation	2733.67	30	66	99
7	VSD patch closure + ASD primary closure + tricuspid annuloplasty	161.17	30	80	102
8	VSD patch closure + PDA ligation	1032.17	32	60	80
9	VSD patch closure	512.50	32	45	59
10	Multiple VSDs; pericardial patch/primary closure + PDA ligation.	624.33	33	80	104
11*	VSD patch closure + ASD primary closure + PDA ligation	4700.00	30	60	85
12	VSD patch closure + PDA ligation	591.67	32	40	54
13	VSD patch closure	266.67	34	87	126
14	VSD patch closure + PDA ligation + tricuspid annuloplasty	727.50	32	53	81
15	VSD patch closure (continuous sutures)	159.00	32	30	45
16	VSD primary closure	441.83	33	23	41
17	VSD patch closure	1261.00	32	27	45
18	VSD patch closure	131.83	28	32	56
19	VSD patch closure + PDA ligation + tricuspid annuloplasty	761.33	31	62	94
20	VSD patch closure	493.17	32	40	58
	Mean	980.05	31.25	56.00	78.2
	Standard deviation	1125.38	1.58	1.63	25.85
	Correlation coefficient for mean postoperative BNP values	–	-0.25	**0.682**	**0.671**
	P value for correlation	–	0.28	**0.001**	**0.001**

BNP: B-type natriuretic peptide; CPB: Cardiopulmonary bypass; VSD: Ventricular septal defect; PDA: Patent ductus arteriosus; ASD: Atrial septal defect; VSDs: Ventricular septal defect.

Table 3. Intraindividual average values of the B-type natriuretic peptide levels and the median values of the postoperative outcome measures

Patient	Mean iBNP value	iBNP-SD	Inotrope score	Time to extubation	ICU stays (day)
1	284.33	159.22	5.00	26.00	3.00
2	2479.67	1544.99	5.00	21.00	3.00
3	934.67	621.52	19.00	48.00	7.00
4	1105.83	370.78	19.00	22.00	4.00
5	198.83	122.14	5.00	5.00	1.00
6	2733.67	1806.79	31.00	120.00	7.00
7	161.17	71.21	0 .00	3.00	1.00
8	1032.17	1066.12	3.00	3.00	4.00
9	512.50	259.71	22.00	24.00	3.00
10	624.33	503.63	8.00	26.00	2.00
11*	4700.00	600.00	16.00	–	2.00
12	591.67	335.98	20.00	24.00	4.00
13	266.67	171.35	0 .00	4.00	1.00
14	727.50	453.86	9.00	22.00	2.00
15	159.00	119.95	0 .00	4.00	1.00
16	441.83	292.30	11.00	4.00	1.00
17	1261.00	1070.32	25.00	200.00	4.00
18	131.83	71.69	6.00	5.00	2.00
19	761.33	684.86	26.00	24.00	5.00
20	493.17	352.07	5.00	24.00	2.00
Median	608.00	361.42	8.50	22	2.50
Interquartile range	271.08-1087.41	162.25-669.02	5.00-19.75	4-26	1.25-4

BNP: B-type natriuretic peptide; i: Intraindividual; SD: Standard deviation; ICU: Intensive care unit; * The patient died on posteoperative second day.

longer ICU stays. Thus, taking this information along with the study outcomes into account, we found that the increased deviations from the mean were strongly correlated with prolonged ICU stays.

Westerlind et al.[11] determined that increased BNP values were associated with both volume overload and abnormal functions in children with CHDs. However, this is a controversial issue because whether or not normal BNP values truly indicate a functionally normal heart is not clear. In addition, it is also not certain whether these values may at least be taken as evidence for the absence of pressure overload. Koch et al.[12] demonstrated in a series of 288 consecutive patients with CHDs that plasma BNP levels do not reflect the extent of the ventricular overload but that they can indicate the presence of ventricular impairment. Cowley et al.[13] also demonstrated that rising BNP levels were well correlated with the degree of left ventricular outflow obstruction, which indicated a linear relationship between plasma BNP levels and the pressure load on the left ventricle. Although a variety of past clinical studies[5,6,12] on BNPs included a mixed population of patients, Kunii et al.[14] demonstrated that BNPs may specifically indicate disease severity

Table 4. Correlation matrix between the intraindividual average values of B-type natriuretic peptide levels and the outcome measures

Variable	Inotrope score	Time to extubation	ICU stay	iCVP-RA	iLactate
Correlation with iBNP-mean					
Coefficient	0.38	0.51	0.30	0.83	0.180
p value	0.09	0.02	0.19	<0.001	0.44
Correlation with iBNP-SD					
Coefficient	0.46	0.57	0.63	0.54	0.12
p value	0.03	0.01	0.003	0.01	0.61

BNP: B-type natriuretic peptide; i: Intraindividual; ICU: Intensive care unit; CVP-RA: Central venous pressure measured at the right atrium; SD: Standard deviation; According to the Bonferroni correction, the *p* value for the limit of significance was p<0.05/6=0.008 for six serial measurements of the BNP.

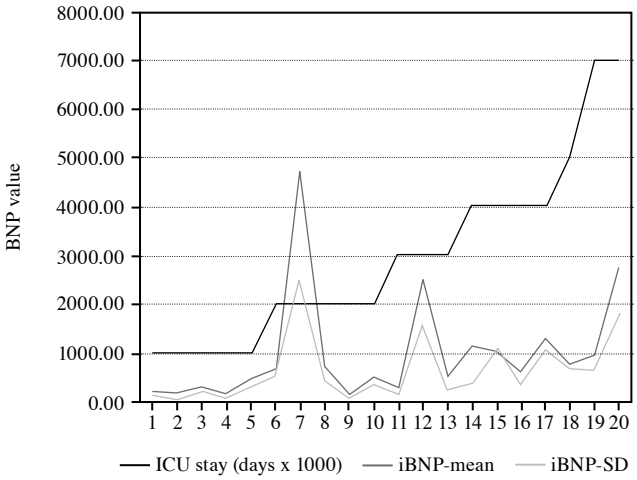

Figure 1. Correlation of intraindividual B-type natriuretic peptide values with the intensive care unit stay duration.

and might have prognostic importance for some common congenital cardiac abnormalities such as ASD, PDA, and VSD. In addition, they determined that the plasma BNP levels were positively correlated with increased Qp/Qs ratios, which is the most widely accepted indication for surgical VSD repair. The latter observation was also supported by Suda et al.[15]

Another of our important findings was that the preoperative BNP values were positively correlated with the mPAP values, although our study was not the first to reporting such a relationship. Suda et al.[15] reported the presence of a positive correlation among the plasma BNP and atrial natriuretic peptide values and pulmonary-to-systemic flow ratios in 59 patients with VSD and also showed that the plasma BNP values above a certain limit (>50 pg/mL) were sensitive to increased mPAP values of >20 mmHg. Furthermore, Mir et al.[16] reported a significant correlation between right ventricular overload and plasma BNP in children with CHDs, although they had no VSD patients in their series. Moreover, Mainwaring et al.[17] estimated an age-adjusted relative risk of 0.33 for the correlation between the BNP values and systemic-to-pulmonary blood flow ratios in children who underwent VSD repair. Finally, Koch et al.[12] demonstrated that the plasma BNP Z-scores of 74 patients with left-to-right shunts (including 35 with VSDs) were significantly associated with higher mPAP values ($r=0.66$; $p<0.01$).

We identified a negative correlation between the patients' body weight and the BNP values, which may suggest that the cut-off values for BNPs vary depending on the percentile of the children with CHDs. Gessler et al.[18] found that there was no significant correlation between body weight and preoperative N-terminal pro-BNP values, but their study group included patients with a wider age range (4-83 months) than ours (5-18 months) and was composed of a mixed patient group. It should also be noted that BNP values are subject to change in normal children, even within the first weeks of life.[19] B-type natriuretic peptides and N-terminal pro-BNPs should be used cautiously in pediatric ICUs because the reference points for neonates and infants differ greatly than those for older children.[6,7,20-23] Therefore, since no adjustment for age and weight was made in our study, our results along with all of the other aforementioned studies except for Mainwaring et al.[17] are subject to criticism.

We also found a significant relationship between the pre- and postoperative BNP values, which was exactly the same conclusion that Mainwaring et al.[17] arrived at in their study. In addition, they also included a group of patients with VSDs, and we both determined that the high preoperative BNP values stayed constant postoperatively, which created an important bias. This correlation seems to be the major

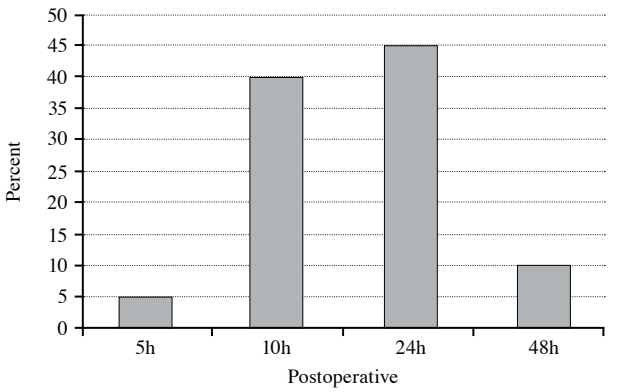

Figure 2. B-type natriuretic peptide peak of the patients according to the length of their intensive care unit stays.

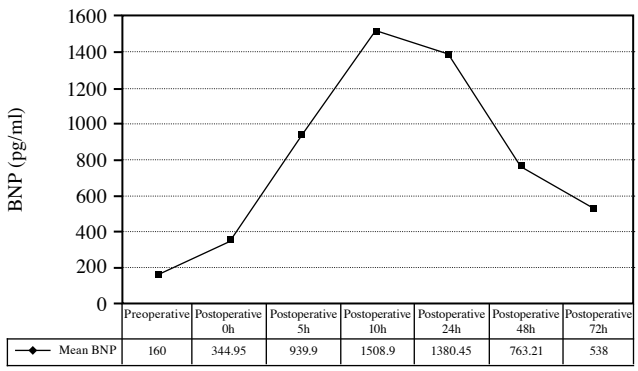

Figure 3. Changes in the B-type natriuretic peptide values during the intensive care unit stays.

drawback for the use of preoperative BNP values as a reliable tool for predicting poor outcomes following VSD repair.

Our postoperative BNP values were also significantly correlated with longer CPB and cross-clamp times, which is in line with Carmona et al.[4] who reported that VSD was present in 15 out of 46 children younger than 18 months in their series. However, Niedner et al.[8] found no correlation between BNP values and CPB times in their study in which 12% of the patients underwent VSD repair. Our CPB and cross-clamp times were close to those reported in these two studies.

Our study had a few limitations. Although the study power was close to the desired level needed to establish a correlation, the sample size of this preliminary study meant that we were limited to performing a multivariate logistic regression analysis because that is an essential tool needed for drawing a definitive conclusion regarding whether intraindividual BNP variability can be used independently for predicting outcomes. Furthermore, although we found no relationship between the other parameters in our study and the outcomes, our small sample size did produce a bias. Therefore, our findings need to be verified by studies that involve a larger number of patients. In addition, the lack of randomization and the fact that we had no control group were also design limitations that might have affected our results.

Conclusion

Our findings indicated that high intraindividual variability in serial measurements of BNPs can potentially predict adverse outcomes after VSD repair. However, further research is needed to confirm whether the availability of BNPs can be used as a surrogate marker for the prognosis of infants who undergo VSD repair.

Declaration of conflicting interests

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