Follow-up papers - Congenital
Levels of N-terminal-pro-brain natriuretic peptide in congenital heart disease surgery and its value as a predictive biomarker

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Abstract

Objective: To explore the value of N-terminal-pro-brain natriuretic peptide (NT-ProBNP) as a predictive biomarker of postoperative cardiovascular surgery. Methods: A prospective study of 68 patients (0–15 years), submitted to open-heart surgery was conducted. NT-ProBNP and other biochemical and clinical markers were measured preoperatively and during the first 48 postoperative hours. Results: NT-ProBNP preoperative reduced one hour after surgery, increased significantly later, and remained without change between 12 hours and 48 hours postoperatively. Peak values (24 hours) were correlated with preoperative levels (R = 0.73; P < 0.001), risk adjustment congenital heart surgery-1 (R = 0.37; P < 0.002), length of cardiopulmonary bypass (CPB) (R = 0.57; P < 0.001), age (R = 0.55; P < 0.001) and weight of patients (R = 0.46; P < 0.001). Independent predictors of NT-ProBNP peak were preoperative value (β = 0.42) and CPB length (β = 0.24; R² of model 0.63; P < 0.001). The peak values were correlated to a maximum inotropic score (R = 0.46; P < 0.001), duration of inotropic therapy (R = 0.44; P < 0.001), duration of mechanical ventilation support (R = 0.39; P < 0.001) and length of stay in the Pediatric Intensive Care Unit (R = 0.45; P < 0.001). Independent predictors of enhanced intensive care unit stay, controlling by risk adjustment score, were high preoperative NT-ProBNP (OR 5.5, 95% CI 1.2–25.5), and high postoperative troponine (OR 10.5, 95% CI 2.2–49.2). Conclusions: NT-ProBNP concentration is dependent on time during the perioperative period, it peaks at 24 hours and depends on the preoperative value and CPB length. A high peptide level before surgery is an independent predictor of prolonged stay in intensive pediatric care.

Keywords: Brain natriuretic peptides; Pediatric open-heart surgery; Postoperative prognostic biomarker

1. Introduction

The brain natriuretic peptide, as the atrial natriuretic peptide, is a cardiac counter-regulatory hormone with diuretic, natriuretic and vasodilatory properties, and is synthesized by the cardiac myocytes in response to volume or pressure overload in order to improve homeostasis. This peptide of 32 amino acids is obtained from an inactive pro-brain natriuretic peptide and NT-ProBNP or N-BNP. There is a 1:1 proportion between the amino-terminal fraction and brain natriuretic peptide, so their concentrations in blood are equal. Unlike the biologically active hormone, NT-ProBNP is more stable and can remain in EDTA for three days at room temperature, or for a longer time at 4 °C or when frozen [1, 2]. Both peptides, the active and the inactive, have been demonstrated to be useful predictive biomarkers for the follow-up of valve disease [3], coronary disease, surgery under cardiopulmonary bypass (CPB) [4, 5], cardiac transplant [6–8] and congestive heart failure in adults. For pediatric patients, the usefulness of brain natriuretic peptide and amino-terminal fraction (N-BNP) has been studied in the evaluation of cardiac dysfunction [9–11], left-to-right shunt, pulmonary hypertension [12, 13], right ventricle volume overload [14] and obstructive lesions [15]. These peptides are beginning to be used as prognostic factors before and after surgery in children with congenital or acquired-heart disease, however, most studies into the value of NT-ProBNP in children after cardiovascular surgery have had a relatively small sample size [2, 16–18].

The main objective of this study was to identify changes of NT-ProBNP levels throughout the perioperative period,
and to characterize the relationship of these values with other demographic, clinical and laboratory parameters. Subsequently, we attempted to explore levels of this peptide as predictive biomarkers of postoperative follow-up features, such as the duration and dose of vasoactive drugs, time of mechanical ventilation, length of stay in the pediatric intensive care unit (PICU), need for extra-renal purification and mortality.

2. Methods

The project was designed as a prospective observational cohort study of pediatric patients under 15 years of age, with congenital heart disease, who were submitted to open-heart surgery. The study was approved by the Hospital Ethics Committee. Informed written consent for each subject was obtained from the parents. Exclusion criteria included previous infection or renal dysfunction. Patients who died during surgery or less than six hours postoperatively were also excluded. Patients who attended the PICU of the University Hospital Madrid-Monterpíncipe between February 2007 and November 2008, and met the entry criteria, were invited to participate. Variables recorded for each patient included: age, weight, gender, main diagnosis, surgical procedure, risk adjustment congenital heart surgery-1 (RACHS-1) [19] score, and CPB time. Follow-up of patients after the surgical procedure included measurements of the duration of mechanical ventilation, the time that inotropic support was required and the highest inotropic score [20, 21], the need for vasodilator drugs, extra-renal purification requirements (peritoneal dialysis or hemofiltration), the length of Pediatric Critical Care Unit hospitalization and in-hospital mortality. The inotropic dosage was calculated according to the following inotropic score: dopamine (μg·kg⁻¹·min⁻¹) + dobutamine (μg·kg⁻¹·min⁻¹) + milrinone (μg·kg⁻¹·min⁻¹) × 15 + (adrenaline + noradrenaline) × 100. Levels of NT-ProBNP were measured in all patients before surgery (24–48 hours), within the first hour after surgery, and at six, 12, 24 and 48 hours after separation from CPB. These measurements were made in our laboratory after blood samples were collected in EDTA tubes from arterial or central venous catheters. The blood samples were immediately processed and frozen at −20 °C. They were measured two to four weeks later using a sandwich immunoassay type electrochemical luminescence (Modular Analytics E170, Roche Diagnostics GmbH, Mannheim, Germany). The technique measurement interval was 5–35,000 pg/ml (range of normality according to age and gender). Simultaneously, troponine T (range of normality, 0–0.04 ng/ml) and lactic acid (range of normality, 0–2.2 mmol/l) values were measured. The preoperative values of the latter parameter were rejected because the samples were not collected from a central catheter.

Distribution of NT-ProBNP perioperative levels were graphically displayed against time. An analysis of variance (ANOVA) for repeated measurements was performed to compare pre- and postoperative NT-ProBNP values. Paired comparisons adjusted by the Bonferroni method were made to compare different pairs of measurements. As age was considered to be a potential confounding variable, all the analyses were adjusted for age, using age as a covariate.

It was verified that the logarithmic transformation of the data followed the assumptions of the ANOVA model, therefore, all analyses were made with the data transformed into logarithms. Maximum levels of NT-ProBNP reached during the postoperative period were considered as N-BNP-peak postoperative values. Preoperative NT-ProBNP and NT-ProBNP-peak postoperative values were either correlated or compared by groups for clinical variables and postoperative follow-up features. Spearman’s correlation coefficients were calculated. In addition, linear adjustments were estimated by linear regression. Multiple logistic regression models with a backward elimination algorithm were developed to determine the best predictors of the postoperative features. Quantitative variables were previously transformed into dichotomized variables at the 75th percentile of its distribution. Odds ratios and 95% CI were computed. All test were considered significant at two-tailed test P < 0.05 value.

3. Results

During the study period, 77 patients met the criteria for entry into the study. Nine patients were excluded, two because their parents refused to give informed consent, and seven due to insufficient laboratory determinations for follow-up. A total of 68 patients, male:female ratio 0.66, aged from days to 15-years-old (median age seven months), were followed-up and evaluated. Median weight was 6 kg (range: 2.2–58 kg). Diagnoses of congenital heart disease and RACHS-1 score at time of surgery are displayed in Table 1. Patients were further classified into three classes according to the predominant physiological category: volume overload or pressure overload (14 patients) and pressure overload or pressure overload (14 patients) and risk adjustment congenital heart surgery-1 (RACHS-1) score category 3.

![Table 1. Distribution of patients by type of congenital heart disease and risk adjustment congenital heart surgery-1 (RACHS-1) score](https://academic.oup.com/icvts/article-abstract/12/3/461/760642/462)
cyanosis (17 patients) (Table 2). CPB time was significantly shorter for the volume overload class than for the other groups. Children belonging to the pressure overload and cyanotic defects classes were younger and weighed less than children in the volume overload group. With respect to the preoperative Pro-BNP levels, differences related to RACHS were found in that the higher the RACHS scores, the higher Pro-BNP levels. Values observed were 2.44 ± 0.48, 2.66 ± 0.86, 3.00 ± 0.95, and 3.78 ± 0.77 for RACHS 1–4, respectively; P = 0.012 (Fig. 1). Nevertheless, no differences were found in NT-ProBNP preoperative levels by physiological class.

Measurements of NT-ProBNP levels immediately before, and one, six, 12, 24 and 48 hours after the surgical procedure are displayed in Fig. 2. Five patients (7%) had preoperative values above the upper limits (97.5th percentile for their age and weight) [22]. In addition, these preoperative values were higher for patients younger than three years of age than for those for patients of three-year-old and older (P < 0.001) (Fig. 3).

Five cases presented with congestive heart failure, and the other had a dextro-transposition of great arteries without congestive cardiac failure. Twenty-five patients were in congestive heart failure before surgery and showed higher values of preoperative Pro-BNP (3.42 ± 0.84 vs. 2.53 ± 0.77; P < 0.001).

NT-ProBNP mean levels before surgery (691 pg/ml) had decreased one hour after the surgical procedure (427 pg/ml), however, this was not statistically significant. Mean levels of NT-ProBNP later increased significantly (P < 0.01 for all comparisons made before or one hour after surgery, with six, 12, 24, or 48 hours after surgery) reaching the maximum 24 hours after surgery (2042 pg/ml) but remaining without significant changes between 12 hours (1698 pg/ml) and 48 hours after surgery (1738 pg/ml). Levels of NT-ProBNP at six hours after surgery were intermediate and significantly different from previous or subsequent measurements (P < 0.01) (Fig. 1). Mean levels of NT-ProBNP before surgery were positively correlated with the length of CPB (R = 0.52; P < 0.001).

NT-ProBNP-peak values (24 h after surgery) were found to be positively correlated with NT-ProBNP preoperative levels (R = 0.73; P < 0.001), RACHS-1 score (R = 0.37; P < 0.002), and length of CPB (R = 0.57; P < 0.001); and negatively correlated with age (R = −0.55; P < 0.001) and weight of the patients (R = −0.46; P < 0.001). Patients in congestive heart failure showed higher values of peak Pro-BNP levels (3.96 ± 0.70 vs. 3.37 ± 0.66; P = 0.001).

Table 2. Age, weight, cardiopulmonary bypass time and preoperative N-BNP levels according to dominant physiological class of cardiovascular defect

<table>
<thead>
<tr>
<th>Age mean (range), months</th>
<th>Pressure overload (n = 37)</th>
<th>Pressure overload (n = 14)</th>
<th>Cyanotic defects (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative NT-ProBNP (log)</td>
<td>2.7 ± 0.7</td>
<td>3.4 ± 1.2</td>
<td>2.8 ± 0.9</td>
<td>0.054</td>
</tr>
<tr>
<td>Weight mean (range), kg</td>
<td>6.8 (3–58)</td>
<td>3.5 (2.2–52)</td>
<td>4.8 (2.7–14)</td>
<td>0.005</td>
</tr>
<tr>
<td>CPB time, min</td>
<td>69.4 ± 38.2</td>
<td>121.7 ± 53.9</td>
<td>114.5 ± 49.5</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>
| NT-ProBNP, N-terminal-pro-brain natriuretic peptide; CPB, cardiopulmonary bypass.
Univariate analysis

Multivariate analysis

Table 3. Predictor indicators of prolonged Pediatric Intensive Care Unit (PICU) stay. Univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 6 months</td>
<td>10.04</td>
<td>2.56–39.36</td>
</tr>
<tr>
<td>RACHS-1 category</td>
<td>3.43</td>
<td>1.54–7.68</td>
</tr>
<tr>
<td>CPB time ≥ 78 min</td>
<td>5.92</td>
<td>1.71–20.54</td>
</tr>
<tr>
<td>N-BNP preoperative ≥ 4.34 log</td>
<td>8.25</td>
<td>2.45–27.73</td>
</tr>
<tr>
<td>N-BNP peak ≥ 4.22 log</td>
<td>12.29</td>
<td>3.47–43.50</td>
</tr>
<tr>
<td>Troponine postoperative ≥ 4.4 ng/ml</td>
<td>7.96</td>
<td>2.30–27.55</td>
</tr>
<tr>
<td>Postoperative lactate ≥ 3.4 mmol/l</td>
<td>6.11</td>
<td>1.91–19.55</td>
</tr>
</tbody>
</table>

RACHS-1, risk adjustment congenital heart surgery-1; CPB, cardiopulmonary bypass.

After adjustment for potential confounding, by multiple linear regression, and leaving only the significant predictors in the model, only two factors were found to be independent predictors of NT-ProBNP peak levels: preoperative N-BNP value (β = 0.42) and length of CPB (hours) (β = 0.24; R² of the model 0.63; P < 0.001).

NT-ProBNP peak levels were found to be significantly associated with selected follow-up features after the surgical procedure. It was found to be correlated with the maximum inotropic score (R = 0.46; P < 0.001), duration of inotropic drug therapy (R = 0.44; P < 0.001), length of supported mechanical ventilation (R = 0.39; P < 0.001) and length of stay in the PICU (R = 0.45; P < 0.001). Furthermore, NT-ProBNP peak was higher in those who required vasodilators (933 ± 1.3 vs. 2754 ± 1.3; P < 0.001). However, NT-ProBNP peak was not found to be associated with the need for extra-renal purification. Compared with surviving patients, those who died (four patients) did not have any significant differences in NT-ProBNP peak levels or in the preoperative Pro-BNP values.

In addition to age less than six months, RACHS-1 category, long CPB duration, and high levels of postoperative troponine and lactate acid, high preoperative NT-ProBNP (upper quartile, ≥3.4 log) and high NT-ProBNP peak (upper quartile, ≥4.2 log) values were found to be associated to an extended PICU stay (more than seven days) by univariate analysis. Multivariate multiple logistic regression analysis revealed that, adjusting for the RACHS-1 category, the most important independent predictors of enhanced PICU stay were high preoperative NT-ProBNP (OR 5.5, 95% CI 1.2–25.5), and high levels of postoperative troponine (OR 10.5, 95% CI 2.2–49.2) (Table 3).

Multivariate analysis could not identify high levels of preoperative NT-ProBNP or NT-ProBNP peak as independent predictors of any of the other postoperative follow-up features.

4. Discussion

In this study we have characterized the variations of NT-ProBNP levels in the perioperative period of children undergoing cardiac surgical repair for congenital defects. We have also attempted to untangle the relationship of NT-ProBNP with other clinical and analytical variables, and to determine the utility of NT-ProBNP as a predictive biomarker of the patients' postoperative follow-up.

This hormone, and its proactive form, increase with the distension of the myocardium and, therefore, with volume overload (cardiac failure; left-to-right shunts) as well as with the ventricular hypertrophy. In adults, it has been proved that cyanoxy increases NT-ProBNP values [23]. Recent studies have focused on finding the real value of these peptides as prognostic factors in pediatric patients submitted to open-heart surgery, comparing them, in some cases, with other more commonly used determinations [2, 11, 16–18]. Our study includes one of the largest sample sizes and the longest period of NT-ProBNP concentration measurement of all the studies published to date.

We observed that, with respect to the timing of the samples obtained, the first value taken after surgery provided no further information and was even lower than the preoperative level. This could be due to the fact that the time that elapses between the separation from extracorporeal circulation and the complete filling of the heart on the one hand, and determination of the NT-ProBNP value on the other hand, is not sufficient to allow the myocytes to liberate the peptide. Avidan et al. showed that the brain natriuretic peptide value decreased markedly when the aortic clamp was applied and the heart was isolated from circulation [24], and that after releasing the aortic cross-clamp there was a slight increase in brain natriuretic peptide concentration, but a more substantial increase occurred two hours after weaning off the CPB. The decrease in the concentration of brain natriuretic peptide, as with the other natriuretic peptides, is supposedly due to rapid removal of the molecule by binding to C-receptors located on endothelial cells. Moreover, Ricci et al. have recently, shown that brain natriuretic peptide is removed by continuous veno-venous hemofiltration in pediatric patients and this effect is comparable to that which occurs when modified ultrafiltration is applied at the end of CPB [25]. As modified ultrafiltration was applied to all of our patients, the slightly low values of NT-ProBNP, a molecule longer than brain natriuretic peptide, found in the immediate postoperative period may also be attributed to the effect of clearance conducted by the CPB and modified ultrafiltration. NT-ProBNP perioperative values begin to increase six hours after surgery, reaching a plateau from 12 hours to at least 48 hours after surgery. Maximum levels are observed 24 hours after surgery. This pattern is in accordance with that obtained by others [16, 17] and it is assumed that this happens when the cardiac output reaches its lowest level after cardiac surgery.

Preoperative levels of NT-ProBNP were positively correlated with length of CPB and length of stay in the critical care unit. These results are in accordance with those of
Walsh and may reflect the severity of the lesion, which in turn leads to greater complexity and duration of the surgical procedure and subsequently to slower recovery.

Maximum NT-ProBNP postoperative levels were found to be highly correlated with several factors. NT-ProBNP-peak value is dependent on preoperative values \((R = 0.73\)\). Age and weight of the patients are also correlated to NT-ProBNP-peak \((R = -0.55\) and \(R = -0.46\), respectively\). The youngest surgical patients usually suffer from more complex cardiac defects, they require longer operations and therefore, experience a higher degree of cardiac stress during the perioperative period. These results are in accordance with those of Carmona et al. in children less than one-month-old, and are explained by the most deleterious effects associated to CPB in this age group.

The longer CPB time correlated with the higher NT-ProBNP-peak \((R = 0.57)\). Presumably, a protracted CPB time causes more severe myocardial injury and impaired cardiovascular function, and therefore, an increase in NT-ProBNP-peak. Notwithstanding, it should be noted that a correlation coefficient \(R < 0.7\), even if statistically significant, shows a moderate strength and should be considered carefully when trying to establish a linear relationship.

Due to the tangled interdependence of all these factors we performed a multivariate analysis to identify the most important independent predictors of NT-ProBNP-peak. Preoperative NT-ProBNP value and the length of CPB were the unique independently associated factors. This suggests that NT-ProBNP-peak is mainly a function of myocardium affection due to the cardiac disease itself, and also to the stress induced by the surgical procedure. Carmona et al. found that a CPB time > 90 min was associated with postoperative low cardiac output syndrome and NT-ProBNP is a biochemical marker of cardiac dysfunction. As suggested by Walsh, who found similar results, inflammation-mediated changes in pulmonary and systemic vascular pressure after CPB can result in an increased myocardial brain natriuretic peptide production and secretion.

NT-ProBNP-peak was also associated with different postoperative follow-up features, such as the maximum dose and the duration of the inotropic treatment, the use of vasodilator drugs, the duration of mechanical ventilation support and the length of stay in the PICU. This last association could not be found in a smaller study [18], but our results were similar to those found by Walsh et al. [16]. We could not find any association of N-terminal-pro-brain natriuretic peak level with the death of patients or with the need for extra-renal purification treatment, presumably due to the scarce frequency of these events in our cohort.

We developed a multivariate analysis including other potential predictors of prolonged PICU stay, but were unable to establish N-terminal-pro-brain natriuretic peak as an independent predictor, which agrees with Mir’s conclusions [18]. We found that adjusted by RACHS-1 score, high N-terminal-pro-brain natriuretic-preoperative levels and high postoperative troponine levels were the most useful independent predictors of an extended stay in the PICU. Walsh et al. found preoperative N-terminal-pro-brain natriuretic to be a moderate predictor of days spent in the PICU, but they did not take into account any other biochemical markers, such as troponine or lactate. Carmona et al. compared N-terminal-pro-brain natriuretic peak with other markers, including troponine, however, they did not analyze the association with PICU stay. We found that the ability of NT-ProBNP-peak to predict lengthened intensive care unit stay is limited, and no better than that of troponine. One limitation of this study is the lack of sufficient power to assess the potential of this biomarker as a clinical predictor. This task would require a multicenter study with a larger sample size.

In conclusion, we have corroborated the time dependence of NT-ProBNP concentration during the perioperative period. We found that NT-ProBNP peaks at 24 hours, and that this peak level is dependent on the NT-ProBNP preoperative value and the time under CPB. Nevertheless, NT-ProBNP is limited in its ability to predict clinical outcomes in this pediatric population and its true value as prognostic factor has yet to be defined.

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References


