Correlation between amino-terminal pro-brain natriuretic peptide levels and the maximum vasoactive-inotropic score in the first 24 h post-intervention of cardiac surgery

Correlación entre los valores séricos de NT-proBNP y el puntaje inotrópico vasoactivo máximo en las primeras 24 horas después de una intervención de cirugía cardíaca

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Abstract

Introduction: The clinical utility of brain natriuretic peptide (amino-terminal pro-brain natriuretic peptide [NT-proBNP]) as a prognostic marker in pediatric patients with heart failure is controversial. The maximum vasoactive-inotropic score at 24 h after cardiac surgery in pediatric patients is an important predictor of morbidity and post-operative mortality. **Objective:** The objective of the study was to determine if there is a correlation between the serum levels of NT-proBNP and the maximum vasoactive-inotropic score at 24 h after cardiac surgery in pediatric patients seen in the intensive care unit. **Materials and methods:** This was an analytical cross-sectional study. A Spearman correlation analysis (r_s) was performed between the serum level of NT-proBNP and the maximum inotropic score both taken at 24 h postoperatively. $p < 0.05$ was considered statistically significant. **Results:** Forty patients were included, 52.5% to the male sex, 72.5% were older than 1 year of age at the time of surgery. A low correlation ($r_s = 0.26$) was found between the serum levels of NT-proBNP and the maximum vasoactive-inotropic score at 24 h, this correlation was not statistically significant ($p = 0.09$). **Conclusions:** To our understanding, the present study is the first to investigate whether there is a correlation between these markers, so our results could set an important precedent that marks the beginning of multiple investigations in our critically ill patients to establish new diagnostic, prognostic, and therapeutic approaches.

Key words: Inotropic score. Brain natriuretic peptide. Correlation. Cardiac surgery. Children.

Resumen

Introducción: La utilidad clínica del péptido natriurético cerebral (NT-proBNP) como marcador pronóstico en pacientes pediátricos con falla cardíaca es controversial. El puntaje inotrópico vasoactivo 24 horas después de la operación cardíaca

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en pacientes pediátricos es un importante predictor de morbilidad y mortalidad posoperatoria. **Objetivo:** Determinar si existe correlación entre los valores séricos de NT-proBNP y el puntaje inotrópico vasoactivo a las 24 horas posteriores a la intervención cardíaca en pacientes pediátricos atendidos en una unidad de terapia intensiva. **Material y métodos:** Estudio transversal analítico. Se realizó un análisis de correlación de Spearman (r_s) entre la cifra sérica de NT-proBNP y el puntaje inotrópico máximo tomados ambos a las 24 horas del postoperatorio. Se consideró estadísticamente significativo un valor de $p < 0.05$. **Resultados:** Se incluyó a 40 pacientes, 52.5% del sexo masculino, 72.5% era mayor de un año de edad al momento de la operación. Se encontró una baja correlación ($r_s = 0.26$) entre las concentraciones séricas de NT-proBNP y el puntaje inotrópico vasoactivo máximo a las 24 horas; dicha correlación no fue estadísticamente significativa ($p = 0.09$). **Conclusiones:** Este estudio es el primero en investigar la correlación entre estos marcadores y los resultados podrían sentar un antecedente que marque el inicio de múltiples investigaciones, con la finalidad de establecer nuevas herramientas diagnósticas, pronósticas y terapéuticas.

Palabras clave: Puntaje inotrópico. Péptido natriurético cerebral (BNP). Correlación. Cirugía cardíaca. Niños.

Introduction

The most common congenital malformations are congenital heart diseases, with a worldwide prevalence ranging from 2.1 to 12.3/1000 live births. In this country, as cause of children's death, congenital heart disease is ranked sixth in children younger than 1 year and third in children aged 1-4 years¹.

Patients who are bearers of congenital heart disease are at high risk of diagnostic delay, given that in primary care, there are not always pediatric cardiologists or basic diagnostic testing available and this makes it difficult for treatment to be implemented in a timely manner. Congenital heart diseases represent a real challenge because they comprise a heterogeneous spectrum of diseases². Diagnostic delay may result in an increase in mortality and morbidity.

Overtime, biomarkers have been found that allow cardiovascular diseases to be detected in a timely manner and gain an advantage before the appearance of clinical manifestations and this way generates a favorable effect on the outcome of this anomaly³.

Cardiac biomarkers with either pre-operative or post-operative predictive capability, which can be used as predictors of cardiac adverse effects in comparison with other common methods, are currently being investigated⁴. There are various biomarkers in the context of cardiovascular disease that provides information concerning the pathogenesis of heart failure by being segregated in a dependent form of the stimulator or initiator event and that, therefore, helps both to identify individuals at risk of developing heart failure and risk stratification; in addition, they have been used as a diagnostic tool or to help in patient monitoring or surveillance³.

According to the European Society of Cardiology and the European Society of Anesthesiology guidelines, the use of type-B natriuretic peptide (BNP) or amino-terminal

proBNP (NT-proBNP) is recommended as pre-operative tests in high-risk heart diseases⁵⁻⁸. Palazzuoli et al.⁹ proposed the use of an inotropic score to measure cardiovascular pharmacological support provided to pediatric patients after a cardiac procedure. This score was derived from empirical data as a measure of the seriousness of the disease^{10,11}.

Materials and methods

An analytical, retrospective cross-sectional study was conducted. NT-proBNP measurement was carried out in pediatric patients aged from 1 month to 16 years 24 h after having undergone congenital heart disease correction at the tertiary care pediatric hospital, from January 1, 2015, to May 15, 2016, as part of the surveillance of some pediatric patients undergoing heart surgery. Sampling was non-probabilistic, of consecutive cases. Patients with acute kidney failure were excluded according to the pRIFLE criteria, before NT-proBNP measurement, as well as patients who required vasopressor support due to septic shock. A descriptive analysis was carried out using simple frequencies and percentages for categorical variables and medians according to NT-proBNP serum values with respect to the different clinical subgroups of included patients. Serum NT-proBNP figures and vasoactive-inotropic score distribution were of the non-parametric type according to their assessment by histogram and with normality tests such as Shapiro-Wilk and Kolmogorov-Smirnov tests, where $p < 0.05$ for these variables. Subsequently, a Spearman correlation analysis was performed between NT-proBNP serum value and maximum inotropic score at 24 h postoperatively, with a statistically significant correlation being considered with $p < 0.05$. To interpret the degree of correlation between the study variables, the following classification was used: (a) if the obtained

Figure 1. Vasoactive-inotropic score.

correlation coefficient was 0-0.2, then the correlation is minimal; if it is from 0.2 to 0.4, there is low correlation; if it ranges from 0.4 to 0.6, then it is a moderate correlation, and from 0.6 to 0.8, it is a good correlation; finally, between 0.8 and 1 corresponds to a very good correlation¹².

Results

Forty pediatric patients under the care of the pediatric intensive care unit (PICU) of the National Medical Center *Siglo XXI* Pediatrics Hospital of the Mexican Institute of Social Security who underwent heart procedures were included, out of whom 52.5% (n = 21) corresponded to the male gender and 47.5% (n = 19) were female; 27.5% (n = 11) were children younger than 12 months (0-12 months), 70% (n = 28) were between 12 and 72 months old, and 2.5% (n = 1) was older than 6 years at the moment of the procedure. For pre-surgical risk stratification, the RACHS-1 2002 scale was used; 57.5% (n = 23) corresponded to risk Group 2, 40% (n = 16) to risk Group 3, and only 2.5% (n = 1) to risk Group 4. A proportion of 87.5% (n = 35) of patients required cardiopulmonary bypass. In 27.5% (n = 11), cardiopulmonary bypass time was < 140 min, and in 72.5% (n = 29), > 140 min. General description of the population and NT-proBNP serum values are presented in [table 1](#).

Of the total population, 77.5% (n = 31) required aortic clamping, with a clamping time > 60 min in 75% (n = 30), with cardiac arrest in 10% (n = 4) of total population.

Serum lactate ranged from 0 to 3 mmol/L in 27.5% (n = 11) of the patients; in 55% (n = 22), it ranged from 3 to 6 mmol/L, and 10% (n = 4) had values > 6 mmol/L. At 24 h of the post-surgical period, 85% of patients (n = 34) had serum lactate levels ranging from 0 to 3 mmol/L, 12.5% (n = 5) showed lactate values ranging from 3 to 6 mmol/L, and 2.5% (n = 1) had a lactate value > 6 mmol/L.

The amines and vasopressors used were dobutamine, norepinephrine, levosimendan, adrenaline, and milrinone. In 12.5% (n = 5), dobutamine was used, 30% (n = 12) of the population required norepinephrine, 20% (n = 8) was treated with levosimendan, and 52.5% (n = 19) required aminergic support with adrenaline. In 50% (n = 20) of the population, milrinone was administered.

Median inotropic score was 5.5 points, with an interval of 0-80 points. Up to 52.5% (n = 21) had an inotropic score < 10, 20% (n = 8), 10-14, 10% (n = 4), 15-19, 2.5%, between 20 and 24, and 15% of patients > 25 ([Fig. 1](#)).

Median vasoactive-inotropic score was 12.5 points, with an interval of 0-97.8 points; 45% (n = 18) had a score < 10, 17.5% had a score of 15-19, 7.5% (n = 3), a score from 20 to 24, and 25% (n = 10), a score > 25 ([Table 2](#)).

Of note, 15% (n = 6) of the patients suffered some type of cardiac arrhythmia during the first 24 h of the post-operative period: bigeminisms, 2.5% (n = 1); atrio-ventricular block, 2.5% (n = 1); ventricular fibrillation, 2.5% (n = 1); and ventricular tachycardia, 5% (n = 2). Cardiorespiratory arrest occurred in 12.5% (n = 5) of the patients. Finally, 5% (n = 2) of the patients died during their stay at the PICU after 24 h of the intervention.

The variables to be correlated in this study were NT-proBNP serum values (mg/dL) and the vasoactive-inotropic score, which showed a non-parametric distribution after assessing their distribution using histograms and when using Kolmogorov-Smirnov and Shapiro-Wilk normality tests, where $p < 0.05$ was obtained for each of these variables. Consequently, a Spearman's correlation analysis was carried out, with the correlation being found to be low ($r_s = 0.26$) and not statistically significant ($p = 0.09$) neither was a difference found in NT-proBNP values between inotropic score categories.

Table 1. General description of the population and NT-proBNP serum values

Variables	Total patients included in the study		NT-proBNP serum value (pg/ni)		p*
	n = 40	Percentage	Median	Min-max	
Gender					
Male	21	52.5	8,289	1,114-25,000	0.57
Female	19	47.5	4,725	1,537-25,000	
Age					
< 1 year	11	27.5	9,125	3,080-25,000	0.13
> 1 year	29	72.5	4,800	1,114-24,000	
RACHS-1					
2	23	57.5	8,412	1,114-25,000	0.55
3	16	40	5,448	2,237-25,000	
4	1	2.5	----	----	
CPB					
Yes	35	87.5	5,896	1,114-25,000	0.75
No	5	12.5	8,289	3,080-25,000	
Aortic clamping					
Yes	31	77.5	7,384	1,114-25,000	0.61
No	9	22.5	5,000	1,537-25,000	
Cardiac arrest					
Yes	4	10	11,448	3,645-24,000	0.34
No	36	90	5,448	1,114-25,000	
Dobutamine (first 24 h)					
Yes	5	12.5	5,000	1,114-25,000	0.33
No	35	87.5	10,469	1,537-25,000	
Norepinephrine (first 24 h)					
Yes	12	30	9,047	1,537-25,000	0.67
No	28	70	5,448	1,114-25,000	
Levosimendan (first 24 h)					
Yes	8	20	6,476	1,114-24,000	0.63
No	32	80	6,640	1,537-25,000	
Adrenaline (first 24 h)					
Yes	19	52.5	9,125	1,114-25,000	0.29
No	21	47.5	4,800	1,537-25,000	
Milrinone (first 24 h)					
Yes	20	50	9,912	2,069-25,000	0.13
No	20	50	4,762.5	1,114-25,000	
Post-operative arrhythmia (PICU)					
Bigeminisms	1	2.5			
AV block	1	2.5			
Ventricular fibrillation	1	2.5			
Ventricular tachycardia	2	5			
Supraventricular tachycardia	1	2.5			
None	34	85			
Cardiorespiratory arrest					
Yes	5	12.5	8,289	3,645-10,469	0.84
No	35	87.5	5,896	1,114-25,000	
Death					
Yes	2	5	8,502.5	4,578-12,427	0.87
No	38	95	6,640	1,114-25,000	

PICU: pediatric intensive care unit.

Table 2. Classification of the study population according to the vasoactive-inotropic score obtained in the first 24 h after surgery

Groups	Inotropic-vasoactive score	Number of patients (%)
1	< 10	18 (45%)
2	10-14	2 (5%)
3	15-19	7 (17.5%)*
4	20-24	3 (7.5%)
5	> 25	10 (25%)*
Total		40 (100%)

*Two patients with vasoactive-inotropic score died during their stay at the PICU due to cardiogenic shock, one with a score of 60.5 and the other with a score of 19 within the first 24 h of the post-operative period.
PICU: pediatric intensive care unit.

Discussion

Overtime, biomarkers have been found that allow cardiovascular diseases to be timely detected and achieving an advantage before the appearance of clinical manifestations and thus favorably modify the outcome of this disorder³.

In recent years, higher activity in biomarker research has been identified and in particular for biomarkers related to the prognosis of patients who are bearers of cardiovascular diseases to timely recognize the subgroups of individuals that would benefit from close surveillance or effective therapeutic interventions^{2,3}.

BNP and NT-proBNP plasma concentration elevation after cardiopulmonary bypass has been well established in multiple studies. Sun (2005) and Costello (2004) reported a maximum point at between 12 and 24 h of the post-operative period, which has been correlated both with cardiopulmonary bypass time and serum lactate concentrations.

Gaies et al. demonstrated in 2010 that a maximum vasoactive score during the first 24 h of the post-operative period of a cardiac intervention in pediatric patients is accompanied to a significant degree by an increased risk of an adverse prognosis, higher mortality, prolonged time to first extubation, as well as longer stay at the intensive therapy unit, in comparison with patients with low vasoactive-inotropic scores¹³. Due to these findings, it is highly important to identify new, accessible biomarkers that allow improving the detection of patients at risk of developing complications and gain an advantage before the appearance of clinical manifestations and favorably alter the outcome of this anomaly.

In this research, a low correlation was found (0.26) between NT-proBNP serum values and maximum vasoactive-inotropic score at 24 h; however, this correlation was not statistically significant ($p = 0.09$). This could be due to an insufficient sample size due to retrospective nature of the project, which included every patient who was admitted to the PICU to receive post-operative care after cardiac surgical procedures and who had NT-proBNP values determined. In addition, it can be related to the heterogeneity of heart conditions of varying complexity that was included in this study. It should be noted that this is the first study to report results of the correlation between the vasoactive-inotropic score and a plausible biomarker that more objectively reflects hemodynamic alterations in pediatric patients undergoing cardiac surgical procedures, which is why there are no other studies to compare the magnitude of these results.

It should be noted that the age range of the patients included in the research is different with regard to those described in medical publications since most of the published work focuses on subgroups of newly born and infant patients¹³⁻¹⁶.

When NT-proBNP serum concentrations were compared between different clinical characteristics of these patients, the serum value of this biomarker was identified to be higher in male patients, in children younger than 1 year, with a RACHS-1 of 2, as well as in those undergoing aortic clamping, in subjects with cardiac arrest, in individuals who were administered norepinephrine and adrenaline, as well as in patients who experienced cardiorespiratory arrest or death during PICU stay; however, these results were not statistically significant, and thus, it is suggested to continue conducting research studies with a methodological design and characteristics that provide higher statistical power and to include a larger number of patients to validate these findings. Up to 37.5% of the population attended to each year at the intensive care unit of the authors' hospital corresponds to congenital heart disease correction post-operated patients, with a mortality of 5-10%. It is imperative to reinforce measures and diagnostic tools for the prevention and early detection of complications and improve patient clinical evolution and outcome.

To the best of the authors' knowledge, this is the first study to investigate whether there is a correlation between NT-proBNP values and inotropic score at 24 h of cardiac operation in pediatric patients.

Conclusions

A low correlation between NT-proBNP serum value and vasoactive-inotropic score was identified, but this result was not statistically significant. To our understanding, the present study is the first to investigate whether there is a correlation between these markers, so our results could set an important precedent that marks the beginning of multiple investigations in our critically ill patients to establish new diagnostic, prognostic, and therapeutic approaches.

Limitations of the study

In this study, obtaining a statistically significant correlation between NT-proBNP values and the inotropic score was not possible, probably due to the following factors: it was a retrospective study, with an insufficient sample size, since many medical records did not comply with the necessary patient data required for this study.

Another important factor for the results is the spectrum, so broad and heterogeneous, of the cardiac abnormalities considered in this research project, which ranged from the correction of single congenital heart defects and complex congenital heart disease to palliative procedures. In addition, the wide age range considered for the analysis may have introduced some bias in the results^{4,17}.

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Conflicts of interest

None.

Ethical disclosure

Protection of people and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Calderón Colmenero J, Cervantes-Salazar JL, Curi-Curi P, Ramírez S. Problemática de las cardiopatías congénitas en México. Propuesta de regionalización. Arch Cardiol Méx. 2010;80:133-40.
2. Silberbach M. Accuracy of plasma B-type natriuretic peptide to diagnose significant cardiovascular disease in children: the Better Not Pout Children! Study. J Am Coll Cardiol. 2009;54:1467-75. <https://doi.org/10.1016/j.jacc.2009.06.020>.
3. Saldarriaga Giraldo C, Jiménez Gómez CA, Ramírez Barrera JD, Carmona Gómez MC. Péptido natriurético cerebral: utilidad clínica. Medicina & Laboratorio. 2011;17:127-44.
4. Manea MM, Comsa M, Minca A, Dragos D, Popa C. Brain-heart axis. Review Article. J Med Life. 2015;8:266-71.
5. Yoo B. Clinical significance of B-type natriuretic peptide in heart failure. J Lifestyle Med. 2014;4:34-8. <https://doi.org/10.15280/jlm.2014.4.1.34>.
6. Troughton R, Felker M, Januzzi JL Jr. Natriuretic peptide-guided heart failure management. Eur Heart J. 2014;35:16-24. <https://doi.org/10.1093/eurheartj/ehu463>.
7. Shang C. B-type natriuretic peptide-guided therapy for perioperative medicine? Open Heart. 2014; 5:1:e000105. doi:10.1136/openhrt-2014-000105.
8. Gaggin HK, Januzzi JLR. Biomarkers and diagnostics in heart failure. Biochim Biophys Acta. 2013;1832:2442-50. <https://doi.org/10.1016/j.bba-dis.2012.12.014>.
9. Palazzuoli A, Gallotta M, Quatrini I, Nuti R. Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure. Vasc Health Risk Manag. 2010;6:411-8.
10. Basaran M, Sever K, Kafali E, Ugurlucan M, Sayin OA, Tansel T, et al. Serum lactate level has prognostic significance after pediatric cardiac surgery. J Cardiothorac Vasc Anesth. 2006;20:43-7.
11. Rhodes JF, Blafox AD, Seiden HS, Asnes JD, Gross RP, Rhodes JP, et al. Cardiac arrest in infants after congenital heart surgery. Circulation. 1999;100:194-9.
12. Guía de asociación entre variables (Pearson y Spearman en SPSS). Consultado el 10 de diciembre de 2018. https://www.u-cursos.cl/fac-so/2014/2/SO01007/1/material_docente/bajar?id.
13. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010;11:234-8. <https://doi.org/10.1007/s00540-018-2447-2>.
14. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, Gall C, et al. Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: an analysis from the Pediatric Cardiac Critical Care Consortium and Virtual PICU System Registries. Pediatr Crit Care Med. 2014;15:529-37.
15. Davidson J, Tong S, Hancock H, Hauck A, da Cruz E, Kaufman J. Prospective validation of the vasoactive-inotropic score and correlation to short-term outcomes in neonates and infants after cardiothoracic surgery. Intensive Care Med. 2012;38:1184-90. <https://doi.org/10.1007/s00134-012-2544-x>.
16. Cantinotti M, Giovannini S, Murzi B, Clerico A. Diagnostic, prognostic and therapeutic relevance of B-type natriuretic hormone and related peptides in children with congenital heart diseases. Clin Chem Lab Med. 2011;49:567-80. <http://doi.org/10.1515/CCLM.2011.106>.
17. Malhotra AK, Ramakrishna H. N-terminal pro B type natriuretic peptide in high cardiovascular-risk patients for noncardiac surgery: What is the current prognostic evidence? Ann Card Anaesth. 2016;19:314-20. <https://doi.org/10.4103/0971-9784.179636>.