Factors Associated with Neonatal Arterial Hypertension: Case and Control Study

Articoli originali

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ABSTRACT

Background. Neonatal high blood pressure has been diagnosed more frequently in recent years, and its impact extends to adulthood. However, the knowledge gaps on associated factors, diagnosis, and treatment are challenging for medical personnel. The incidence of this condition varies depending on neonatal conditions. Patients in the Newborn Unit are at increased risk of developing high blood pressure. The persistence of this condition beyond the neonatal stage increases the risk of cardiovascular disease and chronic kidney disease in childhood and adulthood.

Methodology. A case-control study was carried out. It included hospitalized patients with neonatal hypertension as cases. Three controls were randomly selected for each case and matched by gestational age. The variables were analyzed based on their nature. Multivariate analysis was performed using a multivariate conditional regression model to identify variables associated with the outcome. Finally, the model was adjusted for possible confounders.

Results. 37 cases were obtained and matched with 111 controls. In the univariate analysis, heart disease (OR 2.86; 95% CI 1.22-6.71), kidney disease (OR 7.24; 95% CI 1.92-28.28), bronchopulmonary dysplasia (OR 6.62; 95% CI 1.42-50.82) and major surgical procedures (OR 3.71; 95% CI 1.64-8.39) had an association with neonatal arterial hypertension. Only the latter maintained this finding in the multivariate analysis (adjusted OR 2.88; 95% CI 1.14-7.30). A significant association of two or more comorbidities with neonatal arterial hypertension was also found (OR 3.81; 95% CI 1.53-9.49).

Conclusions. The study analyzed the factors related to high blood pressure in hospitalized neonates, finding relevant associations in the said population. The importance of meticulous neonatal care and monitoring of risk factors such as birth weight and major surgeries is highlighted.

KEYWORDS: Hypertension, Prematurity, Bronchopulmonary Dysplasia, Epigenetics, Neonate, Prematurity, Kidney Disease, Blood Pressure

Introduction

With technological advances in neonatal care, Newborn Units (NU) have undergone significant changes, increasing survival in low-weight patients due to prematurity or intrauterine growth retardation. Low birth weight (LBW) is determined to correspond to weights less than 2500 grams (Table 1).

Birth Weight	
Less than 2500 g	Low birth weight
Less than 1500 g	Very low birth weight
Less than 1000 g	Extremely low birth weight

Table 1. Low birth weight classifications. Adapted and translated from Atehortua et al. [1].

In a full-term neonate with birth weight > 2500 grams, nephrogenesis is normal, resulting in a nephron count ranging from 500,000 to 2,000,000 per kidney. However, in patients with LBW, this count is affected, potentially leading to oligonephronia. Thus, infants with birth weights less than 1000 grams may experience a reduction in nephron count of approximately 40% to 50% [1].

This condition of altered nephrogenesis associated with low birth weight predisposes individuals to renal function abnormalities. As a result, various compensatory mechanisms are triggered, such as increased activity of the renin-angiotensin-aldosterone axis and heightened endothelin activity. These changes have highlighted the emergence of various pathologies; one of them is Neonatal hypertension (NH), which has been underestimated compared to other neonatal conditions [1–3].

Ignorance and lack of standardization in measuring blood pressure (BP) have been a challenge in diagnosing and treating NH [2, 4, 5], which has a variable incidence that increases depending on neonatal conditions and comorbidities. Hence, Neonatal Intensive Care Unit (NICU) patients are more likely to develop the said pathology [3, 4, 6, 7]. It has been identified that the persistence of arterial hypertension after the neonatal stage increases cardiovascular risk and can lead to chronic kidney disease in children and adults [1, 8, 9].

The diagnosis of NH is based on identifying systolic and diastolic blood pressure levels that exceed the 95th percentile, adjusted according to the corrected gestational age (Table 2). This is why, when patients are hospitalized in the NU, it enables the monitoring and tracking of these blood pressure readings. If these readings consistently remain elevated in more than 30% of the records, whether they are systolic or diastolic pressures, the association with NH is determined [1–3, 6, 10, 11]. The most commonly used technique for measurement is oscillometry, a noninvasive method, while invasive measurements are reserved for clinically unstable cases. Most cases of NH are asymptomatic, so proper monitoring and timely treatment are essential to avoid serious complications [2, 8, 11].

Furthermore, certain conditions and procedures, such as using umbilical arterial catheters, bronchopulmonary dysplasia, intraventricular hemorrhage, and kidney diseases, are associated with an increased risk of developing high blood pressure (HBP) [5, 9, 10].

Although NH tends to resolve in most infants in the first months of life, its early detection and appropriate management can significantly impact childhood and adult life [1, 12, 13]. A correlation has been observed between HBP records in childhood and the early development of HBP in young adults [1, 12].

Neonatal blood pressure			
Postconception age	**50th percentile**	**95th percentile**	**99th percentile**
Age 44 weeks			
SBP	88	105	110
DBP	50	68	73
MBP	63	80	85
Age 42 weeks			
SBP	85	98	102
DBP	50	65	70
MBP	62	76	81
Age 40 weeks			
SBP	80	95	100
DBP	50	65	70
MBP	60	75	80
Age 38 weeks			
SBP	77	92	97
DBP	50	65	70
MBP	59	74	79
Age 36 weeks			
SBP	72	87	92
DBP	50	65	70
MBP	57	72	77
Age 34 weeks			
SBP	70	85	90
DBP	40	55	60
MBP	50	65	70
Age 32 weeks			
SBP	68	83	88
DBP	40	55	60
MBP	49	64	69
Age 30 weeks			
SBP	60	75	80
DBP	38	50	54
MBP	48	63	58
Age 28 weeks			
SBP	60	75	80
DBP	38	50	54
MBP	45	58	63
Age 26 weeks			
SBP	55	72	77
DBP	30	50	56
MBP	38	57	63

Table 2. Neonatal BP values according to postconceptional age. *SBP (Systolic blood pressure), DBP (Diastolic blood pressure), MBP (Mean arterial pressure). Adapted and translated from Atehortua et al [1].

This study was carried out in the NU of a tertiary hospital, known as a national reference center for the care of this high-risk population. It is essential to highlight the importance of continued research in the population with NH to understand the associated risks better and improve the care and follow-up of newborns with this condition, generating effective strategies for their comprehensive approach.

Materials and Patients

Retrospective Cases and Controls, February 1, 2014 – September 30, 2019.

Study population

Neonates were hospitalized in the last 6 years in the NICU of a tertiary hospital.

Inclusion criteria:

- Case: Diagnosis of NH by pediatric nephrology is based on the following criteria: systolic or diastolic blood pressure that remains ≥ p95 for more than 24 hours, adjusted according to the corrected gestational age, using either intra-arterial measurements or an oscillometric device [14].
- Control: Neonates without a diagnosis of NH.

Ballard stratified random sampling was performed at birth, with a difference of ± one week and by year of hospitalization.

Exclusion criteria: Initially, it was proposed to exclude from the analysis those who presented pathologies incompatible with life; however, during the data collection of the cases and the assignment of controls, these characteristics were not found.

Sample size: Given the low prevalence of NH, a sample calculation was not performed. The cases were enrolled by convenience when they met the inclusion criteria.

Method: 6154 hospitalized newborns were reviewed. Duplicate records were removed. 156 patients evaluated by the pediatric nephrology service were identified, of which 37 were diagnosed with NH. Three controls were randomly selected for each case using random number filters, matching them by Ballard with a difference of ± one week (total: 111) (Figure 1). Once the cases and controls were identified, their electronic medical records related to hospitalization in the NICU were reviewed in detail, recording the variables of interest in REDcap.

For some patients, birth weight (BW), intrauterine growth restriction (IUGR), umbilical catheterization, maternal exposure to medications or psychoactive substances (PS), history of maternal pathology and hypertensive disorders of pregnancy, were missing data. In some cases, information about administering medications to newborns during their stay outside the institution was not obtained.

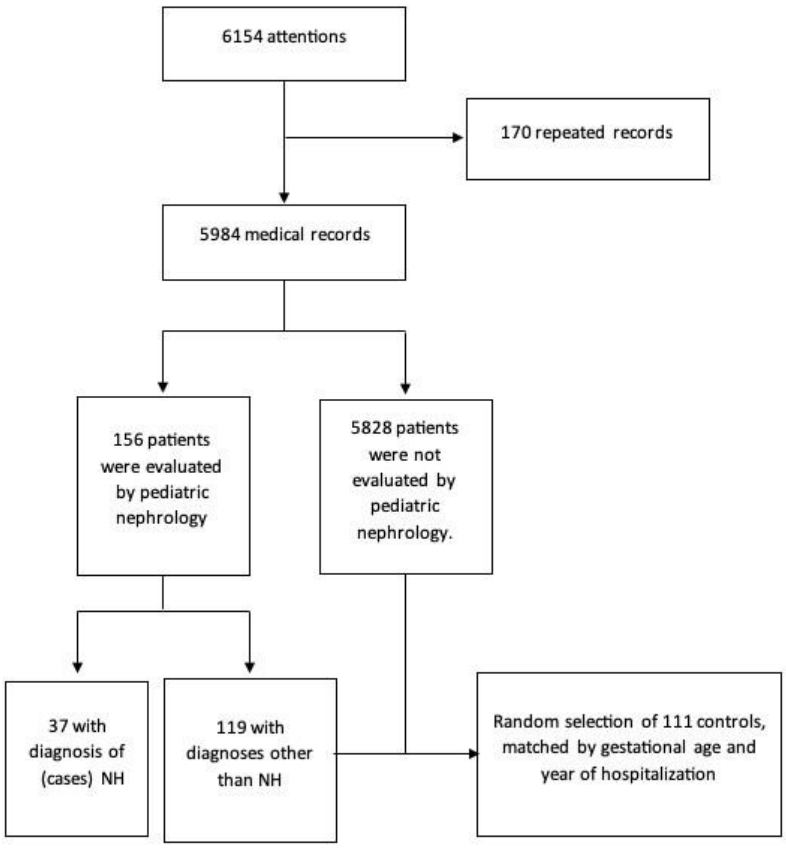

Figure 1. Patient selection.

Statistical analysis

Quantitative variables are shown as central tendency and dispersion measures. For categorical variables, their respective description was made based on exploring the distribution of absolute frequencies between cases and controls. Subsequently, a univariate analysis was carried out for each of the variables to associate them with the outcome of NH, calculating the odds ratio with a conditional regression model and a match ratio between cases and controls 1:3. Variables were considered statistically significant with alpha < 0.05 (newborn comorbidity, major surgical procedure, and BW). Methylxanthine and IUGR were considered possible confounder variables of clinical relevance. A multivariate conditional regression model was implemented to control the potential confusion. The power was estimated for each of the statistically significant variables considered confusing, evidencing the effect of the sample size on the ability to find statistically significant differences.

Ethical aspects

The protocol was approved by the ethics and clinical research committee of Pontificia Universidad Javeriana and the HUSI. The confidentiality of the information was guaranteed. The participation of research personnel is voluntary and does not present any conflict of interest.

Results

62 females (42%) and 86 males (58%) were identified, with no association found between sex and NH (OR 0.93; 95% CI 0.4336-1.98). The minimum Ballard value in both groups was 25 weeks, while the maximum was 38 weeks in cases and 39 weeks in controls. The average BW in the cases group was 950 grams (SD ± 512.9), while the control group was 1097 grams (SD ± 572.3) (Table 3).

VARIABLE	CASES (N 37)	CONTROLS (N 111)
Sex		
Female	16 (43.2%)	46 (41.4%)
Male	21 (56.8%)	65 (58.6%)
Ballard*		
<28 Weeks	18 (48.6%)	36 (32.4%)
28-<32 Weeks	13 (35.1%)	56 (50.5%)
32 to <37 Weeks	4 (10.8%)	13 (11.7%)
≥ 37 Weeks	2 (5.4%)	6 (5.4%)
Birth weight (BW)		
<1000 grams	21 (56.8%)	46 (41.4%)
<1500 grams	10 (27%)	40 (36%)
<2500 grams	3 (8.1%)	16 (14.4%)
≥ 2500 grams	1 (2.7%)	5 (4.5%)
unknown data	2 (5.4%)	4 (3.6%)
Maternal age**	27.7 years (SD ± 6.18)	28.4 years (SD ± 6.87)

Table 3. Demographic characteristics.

9 patients were identified among the cases (24.3%) and 14 among the controls (12.6%) with IUGR. In two cases and two controls, no information was obtained, either by recording the diagnoses in the clinical history or by direct evaluation of the BW (Intergrowth). In this study, no significant association was found with the presentation of NH (OR: 2.15; 95% CI: 0.85-5.43; p: 0.108).

In 16 cases (43.2%) and 37 controls (33.3%), the use of an umbilical catheter (arterial, venous, or both) was confirmed according to the clinical history; however, in 12 cases (32.4%) and 43 controls (38.7%) no information was obtained. When performing the analysis, no significant association was found. Given the more significant correlation described in previous articles between NH and heart disease, bronchopulmonary dysplasia (BPD), and kidney pathologies, these were the three

comorbidities included in the study (Table 4). Within the group of cases, 22 (59.5%) were identified with heart disease, 9 (24.3%) with renal parenchymal disease, 33 with BPD (89.2%) and only 3 (8.1%) without any comorbidity. Of the controls, there were 42 (37.8%) with heart disease, 6 (5.4%) with renal parenchymal disease, 78 with BPD (70.3%) and 29 patients (26.1%) without any comorbidity. In the univariate analysis, three pathologies were associated with the presentation of NH; however, when controlling for confounders or modifying effects, no significant association was found in the multivariate analysis.

VARIABLE	CASES	CONTROLS	OR (95% CI)	p-VALUE
Heart disease	22 (59.5%)	42 (37.8%)	2.86 (1.22-6.71)	0.016
Kidney pathology	9 (24.3%)	6 (5.4%)	7.24 (1.92-27.28)	0.003
DBP	33 (89.2%)	78 (70.3%)	6.62 (1.42-30.82)	0.016

Table 4. Comorbidity by group.

Regarding neonatal administration of methylxanthines, aminoglycosides, or non-steroidal anti-inflammatory drugs (NSAIDs), in 4 cases (10.8%) and 17 controls (15.3%), no data was found in the clinical record. A univariate analysis was performed with the available records without finding a significant association between these medications and NH.According to statements by the World Health Organization, all surgical interventions defined as major surgery were evaluated. Both 15 cases (40.5%) and controls (13.5%) underwent a major surgical procedure. Univariate analysis identified a significant association with NH (OR: 3.712; CI: 1.64-8.39; p: 0.002), which was maintained in the multivariate logistic regression model, controlled by weight and comorbidities (Table 5).

VARIABLE	ADJUSTED OR (95% CI)	p-VALUE
Birth weight	1.00 (0.996 – 1.00)	0.072
Comorbidity	2.12 (0.78 – 5.76)	0.140
Major surgical procedure	2.88 (1.14 – 7.30)	0.026

Table 5. Multivariate analysis controlled by weight and comorbidities.

Route of delivery

Of the cases, 7 (18.9%) were born vaginally and 30 (81%) by cesarean section. Of the controls, 22 (19.8%) were born vaginally and 89 (80.1%) by cesarean section. No significant association was found (OR: 1.06; 95% CI: 0.41-2.75; p: 0.904).

Antenatal maternal exposure to medications or PS, hypertensive disorders of pregnancy, and maternal comorbidities were analyzed. Considerable missing data was shown: 12 cases (32.4%) and 44 controls (39.6%) had no information on medication administration or the consumption of the consumption of the consumption of PS substance consumption; 3 cases (8.1%) and 18 controls (16.2%) had no information on hypertensive disorders of pregnancy; 6 cases (15.2%) and 27 controls (24.3%) had no information on pathological history. With the available information, no significant association was found with NH. No mothers who used cocaine or other PS were identified.

Discussion

The results of this work show an association in the univariate analysis between the presence of heart disease (OR 2.86), BPD (OR 6.62), and kidney pathology (OR 7.24), as well as the performance of the major surgical procedures (OR 3.71) and the presence of NH. These findings correlate with what is described in the literature [9, 13, 15, 18]. However, in the multivariate analysis of these variables, controlled for weight and at least one comorbidity, only surgeries were associated (adjusted OR 2.88). In an additional univariate analysis, patients with two or more comorbidities were found to

have a more significant association with NH (OR 3.81). The data described were obtained from medical record records, which implies some limitations inherent to the methodological design since the quantity and quality of the information found in each record available.

In the literature, gestational age has been identified as a risk factor for developing NH [2, 3, 16, 19, 20]. This study identified that NH occurs primarily in preterm or extremely premature patients (83.7%); most cases had very low or extremely low BW (83.8%). Although the minimum weight value is similar in both groups, the maximum weight value showed a difference, finding an extreme value in the controls due to their random selection process. Additionally, although IUGR is considered a risk factor according to the literature [2, 3, 9, 13], no association with NH was found in this group.

No association was found between the use of umbilical catheters and NH, which could explain the lack of information in the records of patients from other institutions. This factor has been described in other studies not only because it generates a higher prevalence of umbilical artery thrombosis and the risk of thromboembolism in other vessels (25%), but also because there is a direct endothelial injury during catheter passage. Therefore, its implementation per se confers the most significant risk [3, 7, 9, 13, 16, 21].

Although other studies have found associations with maternal diagnosis of hypertensive disorders of pregnancy, maternal exposure to medications, maternal pathological history, and the administration of methylxanthines or nephrotoxic drugs to newborns [1, 3, 9, 12, 13, 16, 17, 20, 21], in this study no such association was found. None of the mothers were PS consumers, so this variable was not analyzed.

Based on this study, it is suggested that patients who present any of the conditions already described should be evaluated and monitored more closely, especially if they undergo major surgical interventions, since, although their pathophysiology may have a multifactorial origin, it is associated with a more significant presence of NH.

Conclusion

Our study sheds light on the factors associated with NH in hospitalized neonates. The importance of careful neonatal care and monitoring of risk factors, such as BW and the performance of major surgical procedures, is highlighted.

Although it is a rarely diagnosed pathology, we collected a sample to analyze the data and obtain significant results on the associated factors.

However, additional research is required to better understand the complex interaction of these factors in developing NH and to improve management and prevention strategies in this high-risk population. The study provides a solid foundation for future research and improvement in care for newborns with NH in newborn units.

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