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ORIGINAL ARTICLE

Prevalence of Arterial Hypertension in a neonatal intensive care unit

Prevalencia de Hipertensión Arterial en una unidad de cuidados intensivos neonatales

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What do we know about the subject matter of this study?

In studies conducted in the United States and Europe, the prevalence of neonatal arterial hypertension (NHT) in neonatal intensive care units (NICUs) varies between 3% and 9%; and occurs predominantly in seriously ill patients.

What does this study contribute to what is already known?

In this study, the prevalence of NHT in the NICU was 4.7% and in all cases, it was presented in premature patients with factors previously recognized as associated with this condition. Therefore, we provide updated information on NHT from Latin America.

Abstract

The prevalence of neonatal hypertension in neonatal intensive care units (NICU) ranges between 3 and 9%. However, there is no current data on Latin America. **Objective:** To estimate the prevalence of neonatal hypertension and to assess its association with causes previously related to this condition. **Patients and Method:** cross-sectional study. All patients admitted to the NICU during one year were included, excluding those transferred to the cardiovascular NICU. The following maternal and neonatal variables were registered: maternal arterial hypertension, type of delivery, gestational age, age, sex, birth weight, Apgar score, history of pulmonary maturation with corticosteroids, and umbilical vessel catheterization as well as the reason for admission to the NICU, medications, and complications during hospitalization. Blood pressure was measured with an automated oscillometric device, defining neonatal hypertension according to standards in gestational age. Prevalence was expressed as percentage (confidence interval 95%, CI95%). Descriptive data were reported as median (range) and frequency of presentation (percentage). Finally, we used the Wilcoxon, Chi^2 o Fisher exact test to identify factors related to NH as applicable ($p < 0.05$). **Results:** 169 patients were included (60% males). Gestational age was 38 weeks (range 26-42 weeks), 38% were preterm. Birth weight was 3000 g (range 545-4950 g) and 32% presented low birth weight. Eight patients presented

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hypertension during hospitalization (4.7% prevalence, CI95% 2.4-9). The presence of hypertension was associated with prematurity (p = 0.0003), low birth weight (p = 0.01), prenatal corticosteroid treatment (p = 0.002), umbilical catheterization (p = 0.03), administration of ≥ 2 nephrotoxic drugs (p = 0.02), caffeine treatment (p = 0.0001), acute kidney injury (p = 0.02), and intracranial hypertension (p = 0.04). Only one patient required antihypertensive pharmacologic treatment and in all cases, hypertension was resolved during follow-up. **Conclusion:** Prevalence of neonatal hypertension in our NICU was 4.7% and in all cases occurred in preterm newborns with previously recognized factors associated with this condition.

Introduction

High blood pressure in children in the neonatal intensive care units (NICU) is an entity that can increase their morbidity and mortality[1,2]. The prevalence of neonatal arterial hypertension (NHT) in NICU is 3%, but in certain conditions, such as bronchopulmonary dysplasia, heart disease, intraventricular hemorrhage, and umbilical vein catheterization, it can reach 9%[3-6].

Other situations that are also associated with a higher prevalence of NHT are the use of prenatal corticosteroids, prematurity, acute kidney injury (AKI), and intrinsic AKI[1,7,8]. This information is based on studies conducted in the United States and Europe, however, there is very little information from Latin America on its prevalence; and, according to our knowledge, there is only one study conducted in Chile in 1987 which reported a 2.5% of prevalence[9].

Due to the technological breakthroughs applied to the care of ill newborns, including the devices used for recording blood pressure (BP), in addition to the availability of charts with BP reference values for this age group[1], knowing the current situation of this condition could be useful in the care of these patients. First, the objective of this study was to estimate the prevalence of NHT in the NICU of our hospital, secondly, we aimed at exploring the association of NHT with causes previously related to this condition, and finally, to describe the treatment and progress of hypertensive patients until the discharge from the NICU.

Patients and Method

Transversal study. We included all patients admitted to the NICU at the Pedro de Elizalde Children's General Hospital from June 1, 2017, to May 31, 2018. This institution admits children with complex pathology referred from other health centers, as well as patients without perinatal history who are admitted due to different intercurrent conditions, mainly infectious. Children with congenital heart diseases requiring transfer to the cardiovascular therapy unit for surgical treatment were excluded.

The following data were recorded from the clinical records and reported by the mother: history of maternal hypertension, delivery route, gestational age, age, sex, birth weight, Apgar score, history of fetal lung maturation with corticosteroids, and umbilical vein catheterization. The reason for admission to the NICU and complications during hospitalization were also recorded, such as hospital-acquired infections, AKI, intraventricular hemorrhage (IVH), and intracranial hypertension (IHT). In addition, it was registered the medication they received, especially nephrotoxic ones (antibiotics, indomethacin, etc.), and other drugs associated with NHT (inotropes, caffeine)[7,10]. A member of the research team recorded daily the BP of all patients according to the protocol by Nwankwo et al[11].

Following the protocol, with the newborn in a prone or supine position, respecting an interval of 1.5 hours after feeding or medical intervention, and with the placement of the appropriate cuff on the right upper arm. Subsequently, the child remained unstimulated for 15 minutes and then, while asleep or awake, three successive BP measurements were recorded at 2-minute intervals. Since the first recording tends to be usually higher, for this study we considered the average value of the three measurements[11].

While other forms have been used to measure BP values in this age group[12], in this study an oscillometric device was used since its determinations are well correlated with the measurement of intra-arterial BP, and the charts of normal values were created based on this methodology[1,7,13].

In the case of patients critically ill, we used the Philips IntelliVue MP40® patient monitor, and in those less critical, the Philips SureSigns VSi® vital signs monitor, because the NICU is physically divided into 2 sectors (high and moderate complexity) and for reasons of asepsis, the devices are not exchanged between these areas. Both devices use the oscillometric method with gradual deflation, share the cuffs, and are from the same manufacturer. The monitors were periodically calibrated by technicians from the supplier.

Based on the records obtained, those patients who maintained increased values for 24 hours or more were considered hypertensive, in order to avoid classifying

as such those who had transient increases without clinical significance (e.g. related to crying, feeding, etc.)[1,11]. It is worth mentioning that in addition to the BP measurements stipulated by the study protocol, the nursing staff measured the BP every 4-6 hours, which is the routine assessment of the patients' vital signs in the NICU.

Despite that in this context usually only one measurement is recorded, unlike the three recommended measurements[11], during the study period, there was no attempt to influence or modify the commonly used technique. Moreover, since it has been observed that routine BP measurements made by nurses are often significantly higher than those obtained according to the protocol[11], those patients who presented with HBP records at routine check-ups were repeatedly evaluated by the research team to ensure proper patient classification.

Operational Definitions

- NHT: values of BP > 95th percentile for age and sex as established by Dionne et al, maintained for more than 24 hours[1].
- According to gestational age, patients were classified as term newborns (between 38 and 40 weeks) and preterm ones (≤ 37 full weeks). In addition, the following subcategories of preterm birth were considered: 1) extremely preterm (< 28 weeks), very preterm (28 to < 32 weeks), and moderate or late preterm (32 to < 37 completed weeks)[14,15].
- The birth weight was related to the GA and, based on the national charts, it was subdivided into high weight, adequate weight, and low weight[14,16].
- AKI: it was defined according to modified KDIGO guidelines for neonates based on glomerular filtration or diuresis decrease. We consider Stage 1 AKIs and above[17,18].

Ethical considerations

The study was approved by the Research and Ethics Committees of our institution. Informed consent was obtained from the parents and/or guardians of the patients to include them in this study protocol.

Statistical analysis

The sample size was calculated according to prevalence, which was estimated based on 139 patients, resulting in a 4.5% average of NHT prevalence (95% confidence, 2% accuracy)[1-6].

The continuous variables were not adjusted to normality (Shapiro-Wilk test), so they were expressed as median (range), while the categorical ones were reported according to the frequency of presentation. The BP was measured daily of all the hospitalized children to establish the NHT prevalence, which was expressed as a percentage with its respective 95% confidence interval (95% CI).

To evaluate the association between the selected conditions (sex, prematurity, low birth weight, Apgar score, delivery route, history of maternal hypertension, history of fetal lung maturation with corticosteroids, umbilical vein catheterization, renal pathology, drugs received, hydrocephalus with IHT, and surgical pathology), and NHT, the patients were divided into two groups (with and without NHT).

Since the quantitative variables lacked normal distribution, they were compared using the Wilcoxon test, while the categorical ones were evaluated with the Chi-square or Fisher's test, as appropriate. A $p < 0.05$ value (two-tailed) was considered statistically significant. The data were analyzed with the Statistix 7 software (IBM version; Analytical Software, Tallahassee, FL).

Results

173 patients were recruited, and four of them were excluded due to they were referred to the cardiovascular therapy unit, resulting in a study sample of 169 patients (figure 1). 74% of the patients included born vaginally and 101 (60%) were male. The median age was 8 days (range 1-28 days), with a median gestational age (GA) of 38 weeks (range 26-42 weeks), and 64 (38%) patients were premature. Within the latter, 6 were extremely premature, 15 were very premature, and 43 were moderately and late premature. The median weight was 3,000 gr (range 545-4,950 g) with a distribution of 65.7% for adequate weight, 32% for low weight, and 2.3% for high weight.

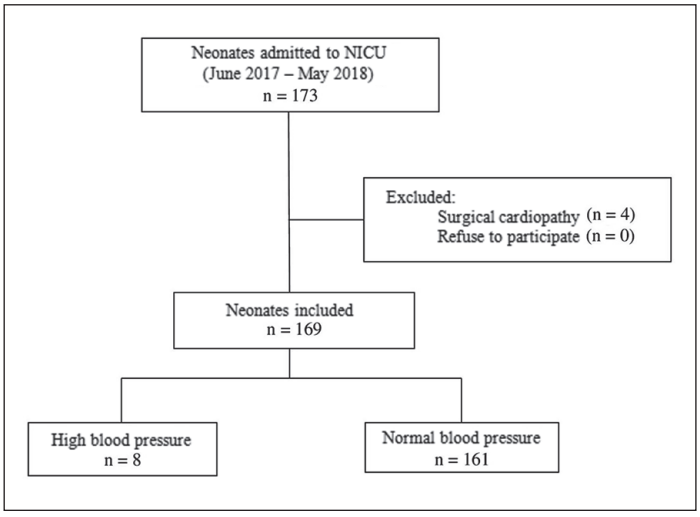

Figure 1. Selection of patients admitted to the Neonatal Intensive Care Unit (NICU).

Table 1 shows the reasons for hospitalization. The most frequent reasons were surgical pathology (41.4%), respiratory intercurrences (19.5%), community-acquired infections (14.8%), and BRUE (Brief Resolved Unexplained Events) in 10.1% of the cases. During hospitalization, the following complications were observed: in-hospital infections (33.1%), development of AKI (17%), IHT (4.7%), and death (4.7%). The prevalence of intraventricular hemorrhage in premature infants was 15.6%, rising up to 33% in patients weighing less than 1,500 g.

Table 1. Reasons for admission to the neonatal intensive care unit

Reason for admission	Patients (n = 169)	
	n	%
Surgical pathology	70	41.4
Respiratory intercurrences	33	19.5
Community-acquired infections	25	14.8
BRUE*	17	10.1
Heart disease	9	5.2
Prolonged jaundice	4	2.4
Metabolic disorders	2	1.2
Myeloproliferative disorders	2	1.2
Other	7	4.2

BRUE: *Brief Resolved Unexplained Events.*

NHT was detected in 8 patients, which represented a 4.7% prevalence (95% CI: 2.4-9). All the cases were premature patients (2 extreme premature, 3 very premature, and 3 moderate and late) hospitalized in the high complexity subsector of the NICU (table 2).

There was a statistically significant association between the development of NHT and the following conditions: prematurity, low weight for gestational age, history of fetal lung maturation with corticosteroids, umbilical vein catheterization, having received ≥ 2 nephrotoxic drugs, development of AKI, presence of ITH, and caffeine administration (table 3).

Three of the hypertensive patients had intraventricular hemorrhage and four had a catheter placed in the umbilical artery. In all cases, the NHT was detected in patients who initially presented normal BP and developed the complication during the hospitalization (table 2). It is worth mentioning that of the 6 patients with NHT who received caffeine, in 4 cases, the increase of the BP occurred during the attack dose and in 2, during maintenance.

Regarding the treatment, only one patient with cerebral edema secondary to kernicterus required enalapril during 3 weeks due to the association of NHT with neurological symptoms; in contrast, all the remaining patients presented a decreased BP with support measures, solving the picture within 72 hours.

Table 2. Demographic and clinical characteristics of patients with neonatal high blood pressure

Case	Sex	Gestational age (weeks)	Birth weight (g)	Reason for admission	Lung maturation	Umblical catheterization	Acute kidney injury	≥ 2 nephrotoxic drugs	Caffeine	Intracraneal hypertension	Treatment
1	F	37	2060	Myelomeningocele	No	No	No	No	No	Yes	VP shunt
2	F	28	590	Intestinal malrotation	Yes	Yes	Yes	Yes	Yes	No	Supportive meausres*
3	M	28	855	Heart disease	Yes	Yes	No	Yes	Yes	No	Supportive meausres*
4	M	30	980	Necrotizing enterocolitis	Yes	Yes	Yes	Yes	Yes	No	Supportive measures*
5	F	37	3240	Kernicterus	No	No	No	No	No	No	Enalapril
6	M	27	730	Omphalocele	Yes	Yes	Yes	Yes	Yes	No	Supportive measures*
7	M	33	1410	Hydrocephalus	Yes	No	No	Yes	Yes	Yes	VP shunt
8	F	26	710	Heart disease	Yes	No	Yes	Yes	Yes	No	Supportive measures*

F: female; M: male; VP: Ventriculoperitoneal. *Dose adjustment or suspension of drugs, volemia correction, analgesia.

Table 3. Associated conditions in patients with neonatal high blood pressure

Characteristic	High blood pressure (n = 8)	Normal blood pressure (n = 161)	p-value
Sex (male/female)	4/4	97/64	0.7
Prematurity	8	56	0.0003
Low weight for gestational age	6	49	0.01
Route of delivery (vaginal/cesarean)	5/3	120/41	0.68
Apgar score at 1 min	7 (6-9)	9 (2-9)	0.16
Apgar score at 5 min	9 (8-10)	10 (5-10)	0.27
Maternal hypertension	-	17	0.6
Lung maturation with steroids	6	17#	0.002
Umbilical catheterization	4	22*	0.03
Intracranial hypertension	2	6	0.04
Acute kidney injury	4	25	0.02
Uropathy	3	23	0.1
≥ 2 nephrotoxic drugs	6	56	0.02
Caffeine	6	6	0.0001
Inotropics drugs	1	21	1
Surgical pathology	5	65	0.27

*Data available in 143 patients. #Data available in 142 patients.

Discussion

In our hospital, the prevalence of NHT in the NICU was 4.7%. This finding is consistent with previous studies that observed a prevalence between 3% and 9% in critically ill patients with multiple associated intercurrences[1-6]. In our series, all the patients who developed NHT shared these clinical characteristics; however, the design of this research allows evaluating association but not causality. Anyways, since they are critically ill children, we could suppose that the NHT is of multifactorial cause. According to this, Dionne and Flynn recently observed that 75% of the patients with NHT in the NICU were premature children with the complications typical of this age group[19].

In our patients, both prematurity and low weight were significantly associated with the development of NHT. The kidney finishes developing at the end of the third trimester of pregnancy, so it is especially exposed to altering its normal development in case of prematurity. This situation can condition, among other consequences, a lower renal mass function and microvascular changes that represent a high risk of HBP, and chronic kidney disease in the long term[20], as it was already proved in epidemiological studies[21,22]. In addition, lower renal mass determines higher susceptibility to the development of AKI in hypoxia/ischemia events and exposure to nephrotoxic drugs[23]. Therefore, despite having solved the events associated with NHT, this group of children requires long-term follow up[20,24,25].

Umbilical vein catheterization, especially that of umbilical arteries, is one of the greatest risk factors for NHT. Watkinson highlights that such procedure could be related to 80% of NHT cases up to the first 2 weeks of life[3]. Although the rate of intravascular coagulation does not exceed 25%, other mechanisms such as endothelial activation with associated vasoconstriction could contribute to the development of NHT[19,24]. Four of the eight hypertensive patients in our series had history of umbilical vein catheterization and, although in them no renal vein thrombosis was detected by Doppler ultrasound, it is known that this is an inconstant finding[1,19].

Mohammed et al. observed that 2.5% of the patients who received caffeine developed NHT, a finding that was not related to the dose used[26]. In our series, 6 of the 12 patients who received caffeine for apnea treatment developed NHT; in 4 of them, it occurred while receiving the attack dose and in the remaining 2 under maintenance dose. None of these children reached the 99th percentile of BP and all of them remained asymptomatic. The records were normalized when the drug dose was decreased or when it was suspended.

In our series, the prevalence of AKI was 17%, a

finding presented in all cases in critically ill premature patients. Remarkably, half of the patients in our series with NHT presented AKI during hospitalization. As already mentioned, these patients are especially susceptible to kidney damage due to their low renal mass, in addition to the severity of their clinical condition and the overlapping of risk factors during hospitalizations, which are usually prolonged[19]. In line with the above, Shalaby et al recently demonstrated that the main risk factors associated with this condition are GA, low birth weight, exposure to nephrotoxic drugs, and sepsis[27].

Certain kidney and urinary tract structural malformations, such as polycystic kidney disease or severe uropathies, are usually concomitant with NHT[1]. Although in our case 15% of the patients presented kidney and urinary tract congenital malformations, most of them were mild (more frequently pyelocalyceal dilatation) and, consequently, they presented normal BP.

Regarding the pharmacological treatment, there is no consensus as to the optimal time to start it[14,22,27]. In asymptomatic patients with BP between 95th and 99th percentile, we will seek to correct the coadjutant factors such as hypervolemia, adjustment of nephrotoxic and inotropic drugs, and pain management; reserving pharmacological treatment for cases where the BP reaches the 99th percentile[14]. The choice of the drug in these cases is also controversial since most of them are not approved for use in neonatology which could explain why between 18 and 25% of the patients with NHT do not receive antihypertensive medication[19].

In our experience, 2 patients with severe hydrocephalus and IHT presented BP records higher than the 99th percentile. Given the emergency, we performed a drainage stabilizing BP until the definitive ventriculoperitoneal shunt. In the rest of the cases, we adopted general measures, such as the adjustment of nephrotoxic drugs when coinciding with AKI, a decrease or suspension of caffeine dose, diuretics to reduce hydrosaline overload, and analgesia in the case of a child in the immediate post-operative period of omphalocele. Only one girl diagnosed with kernicterus required antihypertensive medication, which was maintained for 3 weeks. Although in most cases the NHT was a transitory event, as observed in our patients, studies are suggesting that in the long-term follow-up, the prevalence remains close to 1.3%[28].

This study presents as a strength the prospective collection of data with the continuous and systematized recording of the BP measurements by the research team, unlike previous studies in which the methodology of measuring the BP was variable in frequency and recording methodology[3-6]. In addition, it provides current data from our region on this condition that can be useful to emphasize the detection of this pathology as well as for the development of prevention strategies and long-term follow-up of affected patients. On the other hand, a potential limitation of this study is that 41% of the patients were neonates referred for surgical pathology resolution; however, it is worth mentioning that this condition was not significantly associated with the development of NHT. Moreover, the prevalence found is consistent with previous reports of critically ill children and is much higher than the one observed in healthy newborns (0.2%)[2-6].

Conclusions

The prevalence of NHT found in the NICU of our hospital was 4.7% and it affected exclusively premature children with multiple risk factors. While all cases were resolved, our findings reinforce the importance of continuous monitoring of BP in this special group of patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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