REVISTA CHILENA DE PEDIATRÍA
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Rev Chil Pediatr. 2018;89(1):18-23
DOI: 10.4067/S0370-41062018000100018

ORIGINAL ARTICLE

Ambulatory blood pressure monitoring in school children with a history of extreme prematurity

Monitorización ambulatoria de presión arterial en escolares con antecedente de prematurez extrema

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Received: 03-03-2017; Accepted: 31-08-2017

Abstract

Introduction: Extremely premature children have a higher incidence of High Blood Pressure (HBP) and risk of renal damage due to decreased glomerular count with consequent hyperfiltration of the remnants. **Objectives:** To assess the prevalence of altered blood pressure values in outpatient measurement and ambulatory blood pressure monitoring (ABPM) in preterm infants ≤ 32 weeks and/or ≤ 1,500 g birth weight between 5 and 7 years of age, as well as the presence of early renal damage markers. **Patients and Methods:** An isolated measurement of blood pressure, ABPM and laboratory tests (microalbuminuria/creatininuria ratio in an isolated urine sample, serum creatinine, blood urea nitrogen and urinalysis) were performed. **Results:** 30 patients were recruited, of whom valid measurements of ABPM were obtained in 19 cases, of which nine (47,4%) presented some abnormalities, principally nocturnal day/night difference or DIP absent. No abnormal laboratory tests were found. **Discussion:** Our study detected a high prevalence of abnormalities in ABPM principally DIP absence, which has been related to an increased risk of progression to hypertension. The importance of performing ABPM in the study is emphasized in patients with risk factors for developing hypertension in order to detect early alterations and close management and follow-up.

Keywords:
Hypertension;
Premature Birth;
Blood Pressure Monitoring, Ambulatory;
Kidney Function Tests

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Introduction

High Blood Pressure (HBP) is an increasingly common problem in pediatrics, estimating that this pathology affects 2-5% of the pediatric population in the United States, and 6.3% of the Chilean population[1,2] with a progressive increase in its incidence in at-risk population, even reaching 14% in overweight children and 23% in obese children[3-5].

Preterm newborns (PNBs) and those who are small for gestational age (SGA) are particularly vulnerable to the development of HBP. In PNBs there is a premature exposure of organs that are not yet prepared for the extrauterine life, where an early interruption in the vascular tree development results in stiffer and narrower arteries, predisposing to glomerular and endothelial damage, structural alterations which indicate hyperfiltration and an increase in systolic blood pressure (SBP) in adulthood[6-9]. In SGA infants, the exposure to intrauterine stress generates an altered fetal programming that induces various changes at molecular level and systems functioning, such as alteration in renal growth with decrease in the number of nephrons, which would increase the incidence of HBP and the risk of metabolic alterations that are associated with the development of HBP, such as insulin resistance[10-13].

In Chile, there is a follow-up program for extreme PNBs, where the blood pressure (BP) measurement is performed twice a year. The gold standard for the diagnosis of HBP is still the serial measurement of BP during the evaluation, however, the 24-hour ambulatory monitoring of the BP (AMBP) is becoming increasingly important, since when performing serial measurements (every 15-30 min) it is possible to record blood pressure figures in different physiological situations, including night situations. According to the latest international protocols for the management of HBP, AMBP is becoming more and more important, both in the diagnosis and in the follow-up of these patients.

The objective of this study is to evaluate the prevalence of HBP through ambulatory monitoring of blood pressure and the presence of early markers of renal damage in schoolchildren with a history extreme prematurity.

Patients and Method

Descriptive study carried out in the Pediatric Nephrology Unit of Sótero del Río Hospital. Between August 2015 and December 2016, patients from five to seven years old with history of extreme prematurity were recruited, defined as those under 32 weeks or less than 1500g, who attended follow-up polyclinic checkups. The study was approved by the Ethical-Scientific Evaluation Committee of the South East Metropolitan Health Service and the Ethical Committee of the School of Medicine of the Pontifical Catholic University of Chile. Once the consent was signed, the clinical record was reviewed looking for relevant information. An anthropometric evaluation was carried out and was categorized according to body mass index (BMI) and height by age (H/A) according to the norm for the nutritional evaluation of the Ministry of Health of Chile in 2016[14]. Renal function was assessed (complete urinalysis, creatininuria, and microalbuminuria in isolated sample, creatininemia, and blood urea nitrogen), and the creatinine clearance was estimated according to the modified Schwartz formula[15]. An index of microalbuminuria/creatininuria in an isolated sample less than 30 mg/g was considered as normal[16].

The AMBP was performed using Spacelabs Medical monitor 90207/90217. The pressure was measured every 20 minutes during the day and every 30 minutes during the night, these data were subsequently used to calculate averages of pressures, load of BP (percentage of readings with BP above p95, considering less than 25% as normal) and presence of day/night difference of BP (night DIP = [Average daytime BP-Average nighttime BP]/Average daytime BPx100), which should be higher than 10%. When it presents at least one valid measurement per hour and a minimum of valid readings of 65-75%, it is considered as sufficient readings[13]. Masked hypertension was considered a normal clinical BP with AMBP with overload $\geq$ 25% with an average higher than p95, the presence of day and/or night overload were considered in the field of unclassified alterations[16].

The statistical analysis considered a description of the studied population. The categorical variables were presented in frequencies and percentages, while the continuous variables in the median and range, depending on their distribution.

Results

Clinical Characteristics: Thirty patients were recruited, of which 11 AMBP were not valid (due to a period longer than 1 hour without valid records). A total of 19 valid AMBP were obtained, with a median GA of 29 weeks (28-31), birth weight (BW) of 1,230 g (1,000-1,556) and 6.4 years old at the time of control (6 -6, 5). The median BMI was 0.52 SD (0.11-1.58) and the median H/A was -0.78 SD (-1.51 - -0.27). No patient had nephro-urological malformations, 11 had a history of umbilical catheter use in the neonatal period (57.9%) and in only two cases there was a history of high blood pressure values (table 1).

Blood pressure and AMBP: In two patients it was

not possible to obtain clinical pressures values prior to the Holter installation, and out of the 17 who had it, none of them had BP> p90. The average of readings during monitoring was 81.36%. It was evidenced that nine children presented absence of systolic and/or diastolic DIP (47.37%). When assessing the BP load, it was observed that one patient presented nocturnal systolic and diastolic overload and nocturnal average BP above p95; another patient presented diurnal and nocturnal diastolic overload and the last one presented nocturnal diastolic overload. (table 2).

Characteristics of patients with altered AMBP: nine patients had an altered AMBP, with median of BMI 1.4 SD (0.38-3.44), H/A -0.22 SD (-1.55-0.39) and GA of 30 weeks (29-31). Only 2 patients had a history of increased BP in an ambulatory check-up and normal check-ups afterward. Three patients, in addition to absent DIP, had other alterations (N° 10, 13 and 14), in one of them it was found masked hypertension and two unclassified alterations. When assessing the history of these patients, all three used umbilical catheters and none of them presented HBP in routine check-ups. When assessing the nutritional status at the time of evaluation, the three patients had obesity.

Renal function: Laboratory samples were obtained from 17 out of 19 patients. Creatininemia, urea nitrogen, and complete urinalysis were normal in all patients. When evaluating the creatinine clearance, the average value was 95.86 ml/min with a range between 80.5 and 120.8 ml/min. Two patients had creatinine clearance levels under 90 ml/min, with history of umbilical catheter use and without history of increased BP in previous check-ups. The microalbuminuria/creatininuria index was normal in the 16 patients.

Discussion

Schoolchildren with a history of extreme prematurity frequently present alterations in AMBP, despite not having a diagnosis of hypertension. This is especially important since the early screening allows treatment, follow-up, and study before renal parenchymal damage appears[17].

Table 1. Demographic characteristics and ambulatory blood pressure monitoring values of children with a history of extreme prematurity

	Sex	Age	GA weeks	BW g	H/A SD	IMC DE	Umbilical Catheter	High Blood Pressure	History
1	F	6y	30	1270	-0.22	1.4	+	-	Asthma
2	F	6y 7m	27	1250	-0.9	-0.99	+	-	SLI
3	M	7y	31	1360	1.09	1.51	-	-	Asthma
4	M	6y 6m	29	1020	-2.16	0.18	+	-	Hemiparesia, Asthma
5	F	6y 6m	29	1530	-1.76	-0.54	+	-	-
6	F	6y	31	990	-0.1	0.38	-	-	BPD, SLI
7	M	6y	30	1830	-0.44	1.19	-	-	Asthma, SLI
8	F	6y	27	740	-1.47	-1.83	+	-	BPD, Diplegia, Short stature
9	F	7y	28	1070	-0.78	0.04	+	-	BPD
10	M	5y	31	1670	1.25	3.75	+	-	IgA deficiency
11	M	6y	31	1678	-1.04	0.92	-	-	-
12	M	6y	31	1582	0.58	3.44	-	+	Hypothyroidism
13	F	6y 5m	30	1690	0.39	4.61	+	-	Obesity, HPB
14	M	5y	24	790	-1.55	2.33	+	-	BPD, Asthma
15	F	6y 6m	26	970	-1.02	0.34	+	-	BPD
16	M	6y 6m	28	1010	-1.96	-0.68	+	-	BPD, Asthma
17	M	6y 4m	29	990	-1.8	1.66	-	+	HBP
18	F	7y	29	1040	-0.6	0.52	-	-	Astigmatism
19	M	6y 6m	31	1230	-0.59	0.41	-	-	-

Abbreviations: GA: Gestational age; BW: Birth Weight; H/A: height by age; BMI: Body mass index; SLI: Specific Language Impairment; BPD: Bronchopulmonary dysplasia; HBP: High Blood Pressure; IgA: Immunoglobulin A.

Table 2. Outpatient blood pressure measurements (ABPM) of children with a history of extreme prematurity

	Readings (%)	Day p95 mmHg	Night p95 mmHg	Mean day BP mmHg	Mean night BP mmHg	SBP load day/night (%)	DBP load day/night (%)	Night DIP
1	84	123/81	109/67	103/59	94/52	0/0	0/0	-
2	75	123/82	110/76	98/63	85/49	1.9/0	0/0	+
3	75	122/81	108/65	102/63	91/58	2.6/0	5.1/9.1	+
4	88	123/81	108/66	105/64	100/58	2.2/16.7	2.2/8.3	-
5	75	120/80	110/67	94/64	93/62	0/0	3.1/17.6	-
6	75	120/82	108/68	95/57	89/54	0/0	3.6/5	-
7	85	123/74	106/65	104/65	94/54	2.9/9.1	17.6/9.1	+
8	90	122/82	109/67	109/70	97/53	9.1/12.5	6.8/12.5	+
9	83	120/81	106/65	108/70	95/53	11.1/9.1	9.3/9.1	+
10	80	123/74	106/65	105/68	99/61	3/18	17/27	-
11	89	123/81	108/66	106/68	92/57	2.5/0	0/5.9	+
12	94	123/81	108/66	107/67	98/59	0/10.5	4.9/10.5	Diastolic
13	84	120/81	106/65	106/67	99/54	4.9/2.4	31.3/31.3	Diastolic
14	84	123/81	107/65	108/61	109/61	0/37.5	0/25	-
15	80	122/82	109/67	99/64	89/53	3.4/0	0/9.1	+
16	67	124/81	108/66	109/64	93/53	6.3/0	6.3/0	+
17	83	123/81	108/66	108/65	96/57	10.5/5.6	7.9/16.7	+
18	80	124/82	111/67	110/67	100/62	8.8/0	2.9/11.1	-
19	75	123/81	108/66	107/67	90/51	4.1/0	10.2/0	+

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3. Kidney function assessment in children with history of extreme prematurity

	Crea (mg/dl)	Crea clearance (ml/min)	BUN (mg/dl)	Microalbuminuria (mg/l)	Ma/C Index (mg/g)	Complete urinalysis
1	0.49	96.09	12	5.8	4.9	N
2	0.5	94.16	12	3.4	3.2	N
3	0.52	100.87	11	4.1	5.6	N
4	0.48	92.93	12	< 3.0	-	N
5	0.51	93.93	11	< 3.0	-	N
6	0.48	93.79	15	5.7	10.2	N
7	0.47	100.17	11	< 5.0	-	N
8	0.5	89.2	13.1	< 5.0	-	N
9	0.4	120.8	6	5.3	11.8	N
10	0.49	97.77	12	5.1	6.7	N
11	0.51	94.75	14	4.6	6.9	N
12	0.5	91.69	11	< 3.0	-	N
13	0.53	93.51	13.4	62.36	NA	N
14	NA	NA	NA	NA	NA	N
15	0.58	80.46	18.7	5.3	4.8	N
16	NA	NA	NA	NA	NA	NA
17	0.49	91.87	9	7.6	16.6	N
18	0.47	103.69	13.2	7.4	10.1	N
19	0.51	93.94	13.6	< 5.0	-	N

Abbreviations: Crea: Creatinine; Crea Cl: Creatinine Clearance in isolated sample; BUN: blood urea nitrogen; Ma/C: Microalbuminuria/ creatininuria; N: normal; ND: Non available.

It is also remarkable that, although HBP in pediatrics is less prevalent than in adults, the early detection becomes more relevant, since it has been demonstrated that BP values correlate directly with arterial stiffness, target organ damage and changes in the vascular endothelium, with increased thickness[13].

In Chile, there are no guidelines that establish the need for an AMBP as part of the study in those cases with a risk factor. According to the latest updates on the use of AMBP in pediatrics, its implementation is indicated in patients with an HBP risk factor[13,18]. Many studies in adults have shown the importance of nocturnal DIP as a predictive factor of HBP progression, risk of target organ damage, cardiovascular morbidity and progression to kidney damage, regardless of whether the blood pressure is normal[19,20].

In pediatrics, there are no studies that show a direct relationship between the absence of nocturnal DIP and target organ damage, but it is suggested that the alteration in the normal variation of pressure during the day would be a risk factor for progression to HBP[20]. A study among school children between 5 and 11 years old showed that those children with low birth weight had a smaller BP decrease during the night versus controls of the same age, although the prevalence of negative DIP was similar[21]. It was found that a high proportion of the patients analyzed had absent DIP (53%), which, according to some authors, would be a risk factor for progression and therefore these patients should have a closer follow-up with frequent analysis of BP and control of cardiovascular risk factors. Additionally, it is remarkable the presence of pathological findings that until now are called "unclassified alterations" which, according to some authors, indicate that it could be pre-hypertension, thus these patients should also have a close follow-up[16].

Limitations

Although it is the first approximation to the study of these patients in Chile, the small size of the sample does not allow to determine causality or direct relation. We believe that due to the importance of this topic, it should be discussed and try to find answers with studies with a larger number of patients, since, according to figures provided by the Department of Statistics and Health Information, in 2014, 250,997 children were born and 3,186 of these were under 32 weeks, which means a large number of patients with the risk factor to have HBP, therefore there must be a strict follow-up of this pathology. To this date, this follow-up does not include performing renal function tests or more specific blood pressure monitoring methods such as AMBP, which would allow directing the study of these patients and an earlier detection. Likewise, local guidelines and tables are required since BP recommendations in AMBP are based on studies with European Caucasian patients, which could affect the accuracy of the target BP[4]. Finally, another limitation was the number of invalid AMBP. There are no data available in the literature of invalid AMBP by age, but it is known that the younger the age, the higher the percentage of unsatisfactory studies. This implies the need to repeat the study many times with the consequent economic and time cost for the patient, his or her family and for the healthcare workers. Despite this, we believe that performing AMBP in this selected group of patients is an interesting tool, which allows identifying at-risk children of developing HBP not detected with conventional blood pressure measurement.

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.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Acknowledgment

Preterm follow up polyclinic, Sótero del Río Hospital.

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