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Effect of Placebo on Ambulatory Blood Pressure Monitoring in Children

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Abstract

Ambulatory Blood Pressure Monitoring (ABPM) has been proposed as a useful tool for more accurately diagnosing hypertension (HTN) and evaluating blood pressure (BP) response in pediatric anti-hypertensive trials. ABPM captures multiple BP measurements during routine daily activities and is thus an excellent method for identifying white-coat HTN. Additionally, ABPM measurements in adults do not demonstrate the placebo effect commonly seen with casual BP measurements although this has yet to be evaluated in children. Therefore, this study sought to assess the effect of placebo on ABPM measurements in children. 141 children aged 5 – 16 years with elevated BP were randomized into a multi-center, single-blind, cross-over trial. Subjects received a placebo pill prior to wearing a 24-hour ABPM at 1 of 2 visits separated by 1 – 2 weeks. Study procedures were otherwise identical at both visits. Mean systolic and diastolic BP for all measured time periods were similar between visits as was the number of children diagnosed with HTN at each visit. Having confirmed HTN at baseline did not affect the impact of placebo on mean BP. If confirmed, this lack of placebo effect on ABPM measurements may allow for the design of direct comparison pediatric anti-hypertensive trials without a placebo arm.

Keywords

hypertension; clinical trial; pediatric; blood pressure; pharmacology

Introduction

Hypertension (HTN) affects 3 – 5% of children and adolescents [1–7]. Since the enactment of the Food and Drug Administration (FDA) Modernization Act in 1997, a number of clinical trials have evaluated the safety and efficacy of various antihypertensive medications in these children. Of the different study designs endorsed by the FDA to study drug efficacy of antihypertensive medications in children, all but one contain some component of placebo comparison[8]. While the use of placebo for the short duration of these trials has been shown to be safe[8], the long-term impact of delaying therapy in hypertensive children is unknown. Thus, children with indications for immediate pharmacologic therapy are typically excluded from these studies[9].

The traditional primary outcome measure for anti-hypertensive trials in children is the change in seated 24-hour “trough” auscultatory blood pressure (BP) measurements after repeated daily dosing. Unfortunately, “trough” BP measurements have several inherent limitations. Between 13–53% of children have white coat HTN [10–12], a condition in which BP elevation is limited to clinical settings. The inclusion of these children in anti-hypertensive trials may negatively bias the results as these subjects were not truly hypertensive at baseline. Additionally, 24-hour trough BP may miss an immediate BP lowering response of medications with time-limited effects. Finally, routine auscultatory BP measurements are highly subject to the placebo effect[13], thus necessitating that a placebo arm be included in most efficacy trials.

Ambulatory BP monitoring (ABPM) has been proposed as an alternate way of assessing BP response in pediatric clinical trials. ABPM captures subjects’ BP in a non-clinical setting multiple times over an extended time period thus allowing one to identify subjects with sustained HTN (as opposed to white coat HTN) accurately for inclusion in the study. ABPM also provides a method to evaluate the duration of effects of antihypertensive medications. Lastly, evaluating the mean of multiple BP readings obtained with ABPM provides a better indicator of the overall variability inherent in an individual’s BP. Better quantification of this variability as mean BP may ultimately decrease the impact that placebo has on BP. The following study was thus designed to measure the effect of placebo on BP measured with ABPM in drug-naïve children with an elevated BP (90th percentile).

Methods

A multi-center randomized cross-over study was performed among five participating sites of the Network of Pediatric Pharmacology Research Units (National Institute of Child Health and Human Development). All study procedures were approved by the local Institutional Review Boards (IRB) of each institution. Written informed consent was obtained from a parent/legal guardian for all subjects. Subject assent was obtained when indicated by local IRB practices.

Study Population

Children aged 5 – 16 years with a history of borderline or significant but not severe HTN who were not receiving antihypertensive medications were eligible for enrollment. Subjects underwent a screening examination with three auscultatory BP measurements using a calibrated aneroid manometer and appropriate sized cuff according to American Heart Association standards[14]. Those with a mean systolic BP (SBP) or diastolic BP (DBP) 90th percentile for age, height, and gender[15], but less than 10 mmHg above the 99th percentile[16] per published guidelines at the time of screening were enrolled in the study. Additionally, subjects with significant dysrhythmias (which interfere with the ABPMs ability to accurately measure BP) and those on medications which alter BP (e.g.

corticosteroids or stimulants) whose dose had been changed within four weeks of study entry were excluded.

Study Procedures

The subjects completed 2 study visits over a 2 week period. At each visit, subjects underwent 6 auscultatory BP measurements using a calibrated aneroid manometer followed by a 24-hour ambulatory monitoring period utilizing the Space Labs 90217 oscillometric monitor (Issaquah, WA). At Visit 1, eligible subjects were randomized to receive a placebo between the auscultatory measurements and initiation of the ABPM at either visit 1 or visit 2. No medications or other interventions were performed between these measurements at the alternate visit. Subjects were informed they would be given a medication that may lower their BP. Neither the parents nor study team; however, were blinded to the fact that the pill was a placebo. Parents were instructed to answer any questions about the pill by saying it “may have an effect on BP.”

ABPM monitors were programmed to measure BP every 20 minutes between 7:00 am and 9:00 pm and every 30 minutes between 9:30 pm and 6:30 am. If a successful BP measurement was not obtained at a scheduled time, one additional measurement was attempted 3 minutes later. Measurements were performed with an 8 mm deflation bleed step. Automatic error control provided case-wise deletion of specific BP readings for SBP over 240 or less than 70 mmHg, DBP over 150 or less than 40 mmHg, MAP over 200 mmHg or less than 40 mmHg, pulse pressure greater than 150 mmHg or less than 20 mmHg, and pulse rate greater than 200 or less than 20. Subjects were instructed to continue normal daily activities excluding those which might damage the monitor such as contact sports and swimming while wearing the ABPM. Daytime and sleep periods were determined by patient diary entry. ABPM studies were considered adequate for analysis if the subject wore the monitor for at least 20 hours, obtained at least 60% of expected readings, and had at least one reading during every clock hour the monitor was worn[17].

Statistical Analysis

Demographic data was summarized for the population. SBP and DBP were calculated for 24-hour, day, and night periods and subjects were considered hypertensive if mean 24-hour SBP or DBP was ≥95th percentile for height and gender[18]. Differences between groups were determined using paired t-tests and McNemar’s test with a $p < 0.05$ considered significant. All analysis was performed with SPSS 19 and SAS 9.2.

Results

A total of 202 children were screened for the study of which 97 were ultimately included in the final analysis (See Figure 1). Approximately 23% of the population who completed the study failed to obtain adequate ABPM measurements at one or both visits with only 86 subjects completing both ABPM readings successfully. Baseline demographics and screening BPs of included subjects are shown in Table 1. Baseline demographics and auscultatory BP values did not differ between those included and those excluded from analysis.

Overall mean 24-hour, day, and night SBP and DBP were similar between visits (See Figure 2). The diagnosis of HTN based on mean 24-hour SBP or DBP was also similar between visits. One-quarter of the population had systolic HTN (26.09% with placebo; 23.91% without placebo, $p=0.62$) and one-tenth had diastolic HTN (DBP 9.78% with placebo; 10.87% without placebo, $p=0.71$). Having a diagnosis of HTN either by mean entry casual BP or ABPM measures obtained without placebo did not change the impact of placebo on

mean BP levels (See Table 2). Similar stratified analyses by age group (8–12 years versus 13–16 years) and obesity status found that neither influenced the impact of placebo on mean BP levels.

Discussion

This study demonstrates that placebo has no impact on mean 24-hour, day, and night BP measured by ABPM in a group of children and adolescents with elevated BP. Additionally, the lack of placebo effect was observed in children with confirmed HTN. These results are similar to observations in adults using ABPM[19], but contrast the noted effect of placebo on casual (office) BP measurements at all ages. The BP lowering effects of placebo on casual BP measurements have been demonstrated in multiple pediatric trials[9]. In fact, experience from one trial suggests that 17% of “hypertensive” children will have a normal BP after one-week of single-blind placebo therapy[13]. This compares to normalization rates as high as 30% in adults[20]. The noted lack of placebo effect on ABPM in adults has led to its utilization as the primary BP measurement in several adult anti-hypertensive trials[21–23]. These trials compare antihypertensive agents without a placebo arm. This ensures that hypertensive adults may participate in clinical trials without the potentially negative effect of delaying therapy.

ABPM offers several advantages for future pediatric antihypertensive trials. Disqualifying subjects with white coat hypertension by ABPM may decrease the number of subjects necessary to prove drug efficacy[24]. ABPM will also identify BP lowering effects which do not persist for a full 24-hour time period and provides an approach to better assess pharmacokinetic-pharmacodynamic relationships [25]. Finally, the majority of anti-hypertensive trials include patients with isolated mild to moderate HTN. Children with secondary hypertension, diabetes, known target organ damage, and severe HTN are traditionally excluded from these studies due to ethical concerns over delaying drug therapy. While children with severe HTN were also excluded from this study, ABPM may provide a tool for evaluating BP response in populations that have previously been excluded from antihypertensive trials due to concerns over the use of placebos.

There are a number of limitations to the current study. Only 79% of the population who completed the study satisfactorily completed the ABPM at both visits. While the procedure was well tolerated, this completion rate is lower than has been previously reported in pediatric studies[26, 27]. Future studies should include procedures for repeating ABPM studies that were deemed inadequate to prevent the loss of subjects due to incomplete data. In addition, casual BP measurements at visit 1 were used to determine subject eligibility and the placebo pill was given after these measurements but prior to initiating the ABPM resulting in an inability to evaluate the effect of placebo on casual BP measurements. Inclusion of this comparison in future studies will verify that the study population is in fact subject to the placebo effect described in the literature. Finally, the study reports findings based on the administration of only one placebo dose. While pharmacokinetic studies often utilize only one dose of medication, most studies evaluating the efficacy of an anti-hypertensive utilize placebo over an extended period of time. The extent to which the results of this study can be generalized to a longer exposure to placebo are unknown.

Despite these limitations, the study represents the first to describe the effects of placebo on ABPM in children with HTN. In addition, the study population was diverse and obtained from multiple study sites thus increasing the ability to generalize these findings to other populations. The multi-site design also demonstrated the ability to use this technology in multi-center studies of children similar to most pharmaceutical trials.

In conclusion, this study provides evidence that ABPM represents an effective tool for measuring BP in pediatric anti-hypertensive trials and supports the potential elimination of the placebo arm in comparative dose studies of anti-hypertensive drugs in children. These studies could potentially include more children with high risk profiles for hypertensive morbidity. Additional studies to confirm these findings and to refine protocols to ensure complete collection of ABPM data in this population are warranted.

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List of Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
BP	Blood Pressure
DBP	Diastolic Blood Pressure
FDA	Food and Drug Administration
HTN	Hypertension
IRB	Institutional Review Board
SBP	Systolic Blood Pressure
yrs	Years

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Figure 1.

Study Enrollment

*Some subjects met more than one exclusion criteria

†Other reasons for exclusion included heart rate <2nd or >98th percentile for age (n=3), significant arrhythmia (n=1), height out of range for published pediatric BP normal values (n=7), and taking anti-hypertensive medications at the time of screening (n=1).

ABPM – ambulatory blood pressure monitoring; BP – blood pressure

Figure 2.

Effect of Placebo on Mean BP by Time Period

BP – blood pressure, SBP – systolic blood pressure, DBP – diastolic blood pressure

Table 1

Baseline Characteristics

Baseline Characteristics (n=97)	
Age, yrs	13 (5–16)
Gender, % Male	56%
Race, %	
African American	48%
Caucasian	46%
Other	6%
BMI percentile, %	
Underweight (<5 th %ile)	1%
Healthy Weight (5 th –<85 th %ile)	27%
Overweight (85 th – <95 th %ile)	8%
Obese (≥95 th %ile)	64%
Screening BP index *	
SBP index	1.01 (0.88–1.14)
DBP index	0.90 (0.63–1.15)

* BP index = mean BP/95th percentile for age, height, and gender

yrs – years; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure

Table 2

Effect of Placebo on ABPM measures among those with HTN

HTN Definition	ABPM Measure	Systolic BP			Diastolic BP		
		Placebo	No placebo	p	Placebo	No Placebo	p
Casual SBP or DBP 95 th %ile [*] (n=63)	24-hour	120.39 ± 11.56	120.97 ± 10.03	0.343	67.94 ± 7.21	68.64 ± 6.07	0.120
	Day	125.37 ± 12.19	124.94 ± 10.81	0.878	72.19 ± 8.10	72.15 ± 6.74	0.694
	Night	110.06 ± 11.42	111.03 ± 10.52	0.360	59.09 ± 6.17	59.69 ± 6.77	0.406
24-hr SBP or DBP 95 th %ile [†] (n=26)	24-hour	129.98 ± 9.69	130.25 ± 9.58	0.642	72.12 ± 8.19	72.57 ± 6.80	0.365
	Day	135.74 ± 10.70	135.40 ± 10.61	0.927	76.94 ± 9.03	76.84 ± 7.25	0.759
	Night	117.40 ± 9.85	118.33 ± 9.60	0.390	61.65 ± 7.10	62.54 ± 7.67	0.283
Daytime SBP or DBP 95 th %ile [†] (n=21)	24-hour	131.04 ± 10.24	132.00 ± 9.38	0.588	73.49 ± 8.08	74.51 ± 6.54	0.317
	Day	137.56 ± 10.31	137.79 ± 10.12	0.895	79.09 ± 8.24	79.20 ± 6.54	0.924
	Night	117.18 ± 10.97	118.60 ± 9.91	0.443	61.83 ± 7.76	63.34 ± 8.42	0.224
Night SBP or DBP 95 th %ile [†] (n=30)	24-hour	128.01 ± 10.38	126.90 ± 11.08	0.787	72.42 ± 7.47	71.41 ± 6.21	0.754
	Day	132.02 ± 12.22	130.60 ± 12.48	0.783	76.51 ± 8.79	74.60 ± 7.09	0.352
	Night	120.26 ± 8.89	118.94 ± 9.52	0.562	64.16 ± 5.85	64.17 ± 6.69	0.856

^{*} At entry visit[†] At visit without placebo

ABPM – ambulatory blood pressure monitoring, HTN – hypertension, SBP – systolic blood pressure, DBP – diastolic blood pressure