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Office blood pressure measurement alone often misclassifies treatment status in children with primary hypertension

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Abstract

Objective—Clinicians frequently rely on office blood pressure (BP) measurements alone to assess hypertension control, despite widespread acceptance of 24-hour ambulatory blood pressure monitoring (ABPM) as the reference standard in the initial diagnosis of hypertension. This study was designed to investigate how often the hypertensive status differed between concurrent office BP versus ABPM measurements, and whether any patient-specific characteristics predict the risk for misclassification by office BP.

Participants and methods—This study evaluated 42 children with primary hypertension who underwent repeated ambulatory monitoring (190 total recordings) with concurrent office blood pressure measurement as part of their participation in n-of-1 trials.

Results—In nearly 40% of the visits, the treatment status by office measurement was opposite to the status by ambulatory monitoring. Office blood pressure underestimated the ambulatory hypertensive status (masked uncontrolled hypertension) in 25% of visits, and overestimated ambulatory blood pressure (white coat effect) in 14% of visits. The difference between office blood pressure and ambulatory monitoring was consistent within patients across repeated visits. Patients whose office measurement under- or overestimated the ambulatory blood pressure at the first visit were more likely to show persistent discrepancy at subsequent visits.

Conclusion—The underuse of ambulatory monitoring in management decisions of children treated for primary hypertension may result in systematic misclassification of hypertension control.

Keywords

pediatric; blood pressure; white coat effect; masked hypertension; ambulatory blood pressure monitoring; n-of-1

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Introduction

Childhood hypertension is a growing epidemic that will likely result in increased adverse cardiovascular outcomes in the United States.[1] Reduction of these outcomes attributable to hypertension is partly dependent on the use of a reliable and valid method to assess blood pressure (BP) control. The most convenient and widely used method is BP measurement in an office setting, but ambulatory BP monitoring (ABPM) has become more common, as increasing evidence suggests that ABPM is a better predictor of BP-related cardiovascular and renal outcomes than office measurements.[2] The US Preventive Services Task Force recommends that ABPM should be considered the reference standard to confirm hypertension in adults.[3]

Despite widespread acceptance of the importance of ABPM in the initial diagnosis of hypertension, subsequent clinical decisions on the efficacy of antihypertensive treatment are often based on office BP alone. Several factors could explain why ABPM is used less often to monitor response to therapy, including convenience, limited access to the equipment and trained personnel, patient acceptance and cost to patients or third party payers. No guidelines currently recommend the routine use of ABPM for follow-up of primary hypertension management. There are limited data in pediatrics to assess whether the added time, cost, and effort of an ABPM would make any meaningful difference in hypertension management compared to using office BP alone.[4–7]

Using ABPM as the reference standard for BP assessment, we investigated whether reliance on office BP measurements alone would have resulted in significantly different management decisions in older children with primary hypertension. We utilized data from a cohort of hypertensive children enrolled in a quality improvement study, which provided repeated 24 hour ABPMs with concurrent office BP measurements. We investigated whether factors such as gender, age, race, BMI, and current antihypertensive medication could predict the difference between the two measurement methods. We also tested whether this difference is consistent within a patient in repeated studies over time (e.g. a patient who exhibited masked uncontrolled hypertension at their first visit might show a predictably similar effect at subsequent visits).

Methods

Data from a series of n-of-1 trials of antihypertensive medications were examined to assess the agreement between office and ambulatory BP. A detailed protocol was published previously.[8]

The ambulatory blood pressure monitor (SpaceLabs Ultralite 90217)[9] was worn on the non-dominant arm, with BP measured every 30 minutes over a 24-hour period. Patient-reported sleep times were used to define awake and sleep periods. Only those recordings with at least one reading per hour for a minimum of 18 hours were considered adequate and included in this analysis. Ambulatory hypertensive status was defined as follows for the purpose of this study: normal if both wake and sleep mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) less than the gender/height based 95th percentile; ambulatory

hypertension if either wake or sleep mean SBP or DBP $\geq$ the 95th percentile. [10, 11] Adult cutoffs were used for patients aged 18 years and older.[12]

At the conclusion of the 24 hour ABPM, the monitor was removed and downloaded at a clinic visit and office BP was measured by one of the investigators or a nephrology nurse blinded to the ABPM measurements. Using an automated oscillometric device (Spot Vital Signs LXi, Welch Allyn),[13] four measurements were taken one minute apart on the right upper extremity using an appropriately-sized cuff, with the patient seated and quiet according to Fourth Report recommendations.[14] The second through fourth readings were averaged to determine the office BP for that visit. For the purposes of this study, normal was defined as SBP and DBP $<$ the 95th percentile; and office hypertension if either SBP or DBP $\geq$ the 95th percentile, or using adult cutoffs for patients aged 18 and above.[14, 15]

The primary outcome was the prevalence of misclassification by office BP, i.e. how often the hypertensive status differed in a given visit based on the office BP versus the ambulatory BP. We tested the predictors of misclassification using a mixed effects logistic regression model allowing for random intercepts by patient, thereby accounting for repeated measures within patients. Regardless of treatment status, masked uncontrolled hypertension was used to denote visits characterized by normal office BP but ambulatory hypertension; and white coat effect referred to visits with hypertension by office BP but with normal ambulatory BP.

We also evaluated the paired BP difference, defined as office BP minus ambulatory wake mean BP. Normality assumptions were assessed visually by histograms. In analyzing the predictors of the magnitude of the paired BP difference, we used linear mixed effects models accounting for repeated measures within patients.

All models included the following univariate predictors: gender, age, race, BMI, and current antihypertensive medication. To test the assumption of linearity, BMI, and age were included as linear as well as categorical predictors in separate models. Two-sided p-values <0.05 were considered statistically significant for all tests.

Informed consent was not required, as the n-of-1 trial protocol was classified as a quality improvement activity by the Committee for the Protection of Human Subjects at UTHealth McGovern Medical School based on the primary goal of improved care for the participant, exclusive use of approved and commonly used therapies, and no anticipated increased risk of harm compared to usual care.

Results

From June 2013 until July 2016, 42 adolescents with primary hypertension took part in n-of-1 trials. Table 1 summarizes the patients' baseline characteristics. Three quarters of the patients were obese or overweight, and the most common comorbidities included obstructive sleep apnea, asthma, allergic rhinitis, and dyslipidemia. Seven patients required only a single ABPM, as they were normotensive after being trialed off medication, and therefore did not require repeated visits. Three patients were lost to follow-up after a single visit. Among the 32 patients who completed repeated visits to test antihypertensive drug efficacy, ABPM was worn a median of six times per patient (range 3–8 per patient). A total of 175 ABPM

recordings were considered adequate as defined in the Methods section and included in the following analysis.

Misclassification of hypertensive status

The hypertensive classification by ABPM was different from the classification by office BP in 38.3% of the visits, $\kappa=0.20$. Masked uncontrolled hypertension occurred in 24.6% of visits, and white coat effect in 13.7% (Table 2). Office BP showed a 64% sensitivity and 57% sensitivity to correctly identify ambulatory hypertensive status.

The frequency of misclassification varied widely among patients, ranging from 0% (no disagreement between ABPM and office BP) to 100%, median 32.5% (Table 3). Patients whose first visit was characterized by misclassification had a high frequency of misclassification at subsequent visits (45%), although those with agreement at the first visit also had high rates of misclassification at subsequent visits (25%); OR=2.03, 95% CI 0.72 to 5.73 for univariate mixed effects logistic regression to predict misclassification. Black patients had a higher rate of misclassification, median 45% compared to 25% in Hispanics; odds ratio (OR) 2.97; 95% CI 1.03 to 8.51 for univariate mixed effects logistic regression to predict misclassification. Gender, age, and BMI did not predict a difference in an individual's risk for disagreement between office BP diagnosis and ABPM diagnosis.

Paired difference between office and ambulatory BP

The paired BP difference was calculated for each visit and each patient by subtracting the ambulatory wake mean BP from the office BP. Figure 1 shows the ambulatory SBP was underestimated by office BP by a margin of 10 mmHg in 25% of visits, and overestimated in 18% of visits.

Patients whose office SBP overestimated ambulatory wake mean SBP at the first visit were more likely to exhibit persistent overestimation on subsequent visits (OR 15.24, 95% CI 1.68 to 138.17) compared to those with underestimation at first visit. In these patients, the mean paired SBP difference on subsequent visits was +4.6 mmHg (95% CI -0.6 to 9.8). The converse was also true, patients whose first visit office SBP underestimated ambulatory SBP were more likely to show persistent underestimation at later visits (OR 13.68, 95% CI 1.26 to 148.22), and ambulatory SBP on subsequent visits was consistently underestimated, mean paired SBP difference -4.3 mmHg (95% CI -8.2 to -0.3).

Younger patients (<12 years old) had a larger difference between office BP and ABPM compared to older patients. Younger children showed underestimation by office SBP (mean -7.2 mmHg; 95% CI -13.3 to -1.0) while older children did not (mean 0.5 mmHg; 95% CI -2.7 to 3.6). Gender, race, BMI, and current antihypertensive medication were not associated with the magnitude of the difference between office and ambulatory BP.

Discussion

In the present cohort of 42 hypertensive children who underwent repeated ABPM paired with office BP measurements, the office BP resulted in a contradictory diagnosis from the ABPM in 38% of visits. To our knowledge, an analysis of repeated ABPM has never

previously been reported in children and the usefulness of routinely repeated ABPM to assess BP control in hypertensive children has not been tested. We found that the difference between office BP and ABPM at the first visit predicted the magnitude of the difference between the two methods at subsequent visits. While patients with misclassification at the first visit had a high rate of misclassification at subsequent visits (45%), those with concordant diagnoses at the first visit also experienced misclassification at their subsequent visits (25%). A future study with a larger sample size could provide a more precise estimate of the incremental increase in risk for misclassification at future visits based on whether it occurred at the first visit. This data could help clinicians judge which patients might benefit more from routine use of ABPM to monitor antihypertensive therapy efficacy.

The current study was underpowered to evaluate the effect of patient-specific characteristics on the disagreement between ABPM and office BP. Specifically, univariate analyses did not show that gender, current medication, or BMI were associated with the magnitude of the paired BP difference. Despite the small sample size, we did find a significant difference by race, with Black patients showing more misclassification than Hispanics. This finding was unexpected and should be examined further with more races represented.

Ambulatory wake mean SBP was higher than office SBP more often in younger patients compared to those aged 12 years and older; but this did not translate into an increased prevalence of masked uncontrolled hypertension in younger patients. This result may be related to increased activity levels in the ambulatory setting in younger patients, which could result in higher ambulatory BP readings that may not be clinically meaningful.

Previous studies in children observed similar overall rates of disagreement between office and ABPM diagnoses. A retrospective review of children with suspected or known hypertension compared ABPM with casual BP readings (not reported whether auscultatory or oscillometric), and found that in 8 out of 20 patients (40%) the management decision based on ABPM was opposite to that predicted by casual BP.[4] A larger, recent retrospective study evaluated the agreement between office BP (auscultatory or oscillometric) and ABPM in 206 pediatric patients who underwent 247 ABPM recordings. Among untreated patients, the office BP resulted in a contradictory diagnosis from the ABPM in 45% of recordings.[6] The ESCAPE trial group showed that among 118 treated hypertensives with chronic kidney disease, 30% had discordant diagnoses by office BP (auscultatory) and ABPM (23% with white coat effect and 7% with masked uncontrolled hypertension). [7]

The main strength of this study was the use of repeated ABPM in children and the large total number of ABPM readings. The study had certain limitations as well, including the use of oscillometric measurements to determine office BP. There are some data to suggest that automated oscillometric measurement in hypertensive adults may correlate better with ABPM than auscultatory BP.[16] However, pediatric normative tables are based on auscultatory measurement, and assessing oscillometric readings according to these tables may be problematic.[14] Another limitation was the racial make-up of our patients, in which white and Asian children were under-represented. The study was performed in a single-center, which may limit the generalizability of the results.

In conclusion, we have shown that the use of office BP to assess hypertensive children on treatment can result in misclassification of BP status. We found that Black children may experience more misclassification by office BP, and this should be studied further. Children who showed under- or overestimation of ambulatory BP by office BP at the initial visit were more likely to experience the same effect at subsequent visits. Future studies should focus on identifying the factors that predict which children would benefit most from the routine use of ABPM in follow-up visits to monitor efficacy of antihypertensive treatment.

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Figure 1.

Paired blood pressure (BP) difference (office BP minus ambulatory wake mean BP) for systolic (Panel A), and diastolic (Panel B). Panel A shows ambulatory SBP was underestimated by > 10 mmHg in 24.6% of visits, and overestimated by >10 mmHg in 17.9% of visits. In Panel B, ambulatory DBP was underestimated in 4.5% of visits, and overestimated in 17.3% of visits.

Table 1

Baseline characteristics of patients

Characteristics	Median (range) or N (%)
Total	42
Age, years	14 (9–21) ^a
Sex	
female	16 (38.1%)
male	26 (61.9%)
Obesity*	
Normal/underweight	10 (23.8%)
Overweight (BMI 85 th –95 th %ile)	13 (32.0%)
Obese (BMI > 95 th %ile)	19 (45.2%)
Race/ethnicity	
Hispanic/Latino	23 (54.8%)
Black	17 (40.5%)
White	2 (4.8%)
Co-morbidities	
Obstructive sleep apnea	7 (16.7%)
Asthma	5 (11.9%)
Allergic rhinitis	4 (9.5%)
Dyslipidemia	3 (7.1%)
Attention-deficit hyperactivity disorder	2 (4.8%)
Developmental delay	2 (4.8%)
Single renal cyst	2 (4.8%)
Hypothyroidism	1 (2.4%)
Polycystic ovarian syndrome	1 (2.4%)
Depression	1 (2.4%)

^aFive patients were 18 years of age

^bBy 2000 US CDC Growth Charts [17]

Table 2

Classification of hypertensive status comparing office BP to ambulatory BP at the same visit; 175 visits included (by either systolic or diastolic BP).

		Diagnosis by ABPM	
		Normal	Hypertensive
Diagnosis by office BP	Normal	29 (18.3%)	43 (24.6%)
	Hypertensive	24 (13.7%)	76 (43.4%)

BP, blood pressure

ABPM, ambulatory blood pressure monitor

Table 3

Misclassification of treatment status by office BP, frequency within patients across repeated visits.

	Frequency of misclassification within patients; median (range)
Total (n=32) ^a	32.5% (0–100)
First visit ABPM diagnosis ^b	
Agreement with clinic BP diagnosis (n=20)	25% (0–100)
Disagreement with clinic BP diagnosis (n=10)	45% (20–100)
Gender	
Female (n=12)	22.5% (0–100)
Male (n=20)	40% (0–100)
Age	
< 12 yrs (n=6)	25% (0–80)
>=12 yrs (n=26)	40% (0–100)
Race	
Hispanic (n=19)	25% (0–80)
Black (n=12)	45% (0–100) ^c
White (n=1)	25%

^aExcluding patients who were lost to follow-up before repeated visits could be completed.

^b2 out of 32 not included due to low quality ABPMs at enrollment

^cp=0.043 in a univariate mixed effects logistic regression