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Intensive treatment of clinic BP resulted in lower nighttime, daytime and 24 hour ambulatory BP

Dr. Sanjay M Agrawal

MD DNB (Medicine), Prof. of Medicine at Shri B.H. Government Medical Collage, Dhule, Maharashtra, India

Abstract
Hypertension is considered to be an important modifiable risk factor for cardiovascular events, end-stage renal disease (ESRD), and mortality. In a traditional manner, blood pressure (BP) is measured in the clinic setting using the auscultatory method and a mercury sphygmomanometer. However, technologic advances have led to betterments in measuring clinic BP and allowed for measuring BP outside the clinic. Home BP and 24-hour ambulatory BP have bettered our ability to evaluate the risk of target-organ damage and hypertension-related morbidity and mortality. Measuring home BPs may lead to more active participation in health care by patients and has the potential to improve BP control. Ambulatory BP monitoring enables measuring nighttime BPs and diurnal changes, which may be the most accurate predictors of risk associated with elevated BP. Additionally, reducing nighttime BP is executable and may be an important component of effective antihypertensive therapy. However, in a country like India with constraints in resource setting and poor medical literacy, clinicians still resort to in-clinic BP measurements for management of hypertension. In this review, we aim to have a sneaking look into the available clinical evidence as to how intensive treatment of clinic BP have resulted in lower nighttime, daytime and 24 hour ambulatory BP.

Keywords: intensive treatment, clinic BP, nighttime BP, daytime BP, 24 hour ambulatory BP

Introduction

There is substantial evidence that in-clinic intensive blood pressure (BP) control is a significant predictor for adverse outcomes and can be considered as a reliable measurement in the management of HTN. Even though, clinic-based blood pressures have long been used in clinical trials and the management of patients with hypertension, there has been increasing interest in elucidating how clinic based blood pressures measurements have an impact on BP measured outside the office setting viz. nighttime, daytime and 24 hour ambulatory BP.

Epidemiological studies affirm a continuous, additive risk for cardiovascular (CV) disease, stroke, and renal disease with raising levels of both systolic as well as diastolic BP.[3-4] Usual BP as low to a level of 115/75 mm Hg has a direct relation to mortality attributed to ischemic heart disease, stroke, and other vascular causes. The classic definition of hypertension (HTN) is solely based on in-clinic BP measurements. Most of the evidences associating HTN to CV morbidity and mortality are derived from in-clinic BP measurements. Nonetheless, these office measurements may not reflect true BP levels. Different BP measurements monitoring techniques have been put forwarded a precise technique used to quantify BP levels and diagnose HTN. Recent studies have proven that 24H ABPM is more accurate than office BP measurements in predicting CV morbidity and mortality [5-9]. A distinguished feature of ambulatory BP compared with traditional clinic-based measurement is its ability to assess BP throughout the day and night in the background of usual activities, rather than at a single time point in the clinician's office. Similarly, a plethora of observational studies have demonstrated the superiority of night-time BP as a better predictor for clinical outcomes than that of daytime and office based BP measurements.

Clinical Evidence

All large scale randomized trials conducted in hypertension have employed clinic-based BP to determine qualifying criterion for participation in the HTN trials as well to direct antihypertensive drug therapy. The effect of clinic-based hypertension treatment on ambulatory BP is not well studied. Hence, Mancia *et al*. had carried out a meta-analysis of clinical trials by assessing ambulatory BP at baseline and that after an intervention. They demonstrated that reduction of every 10 mmHg decrease in clinic systolic BP, ambulatory systolic BP decreased by 4.2 mm Hg only [10]. Even a little is cognized about the consequence of targeting different levels of clinic BP on measures of ambulatory BP. In the landmark HOT trial (Hypertension Optimal Treatment), which targeted three different levels of clinic diastolic BP, no difference was found with regards to 24-hour ambulatory BP between the treatment arms [11]. This may be attributed to the small differences in achieved clinic diastolic BP between the three arms of the study. However, still there were limited evidences on the effect of targeting different levels of clinic systolic BP on ambulatory BP. Hence, if a lower treatment goal has to be more broadly incorporated into clinical practice, it is important to understand the effect of intensive clinic-based BP lowering strategies on ambulatory BP. In this background, the SPRINT (Systolic Blood Pressure Intervention Trial) trial was conducted. It was a large multicenter, randomized, controlled trial in a total of 9361people with a systolic BP of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes mellitus or prevalent stroke. The results from the SPRINT elicited significant reductions in cardiovascular events (25%) and mortality (27%) with treatment of clinic systolic BP to a target of <120 mm Hg (intensive treatment) compared with a target of <140 mm Hg (standard treatment). As mentioned above, the effect of

clinic-based hypertension treatment on ambulatory BP was not well studied. Hence, the investigators had conducted a subset analysis by further measuring ambulatory BP in a set of participants in the SPRINT study at selected clinical sites. The goal of this analysis was to evaluate the difference in nighttime systolic BP, as well as other ambulatory BP-derived parameters (daytime systolic BP, 24-hour systolic BP, night/day systolic BP ratio, and 24-hour BP variability) between the intensive and standard clinic-based BP treatment groups in SPRINT. The investigators obtained the ambulatory BP within 3 weeks of the 27-month study visit in 897 SPRINT participants. *Intensive treatment resulted in lower clinic systolic BP (mean difference between groups=16.0 mm Hg; 95% confidence interval, 14.1–17.8 mm Hg), nighttime systolic BP (mean difference=9.6 mm Hg; 95% confidence interval, 7.7–11.5 mm Hg), daytime systolic BP (mean difference=12.3 mm Hg; 95% confidence interval, 10.6–13.9 mm Hg), and 24-hour systolic BP (mean difference=11.2 mm Hg; 95% confidence interval, 9.7–12.8 mm Hg)*. The night/day systolic BP ratio was similar between the intensive (0.92±0.09) and standard-treatment groups (0.91±0.09). There was considerable lack of agreement within participants between clinic systolic BP and daytime ambulatory systolic BP with wide limits of agreement on Bland–Altman plots. The Bland-Altman plot is a graphical method to compare two measurements techniques. In this graphical method the differences (or alternatively the ratios) between the two techniques are plotted against the averages of the two techniques. In conclusion, targeting a systolic BP of <120 mm Hg, when compared with <140 mm Hg, resulted in lower nighttime, daytime, and 24-hour systolic BP, but did not change the night/day systolic BP ratio. Ambulatory BP monitoring may be required to assess the effect of targeted hypertension therapy on out of office BP. Further studies are needed to assess whether targeting hypertension therapy based on ambulatory BP improves clinical outcomes [12].

Recently, the United States Preventive Services Task Force had made a grade A recommendation for the measurement of ambulatory BP in patients with elevated clinic BP to confirm the diagnosis of hypertension before initiating antihypertensive therapy [13, 14].

This recommendation is based on the evidences generated from observational studies which demonstrated that ≈25% of patients with elevated clinic BP have normal BP outside the clinic, known as white-coat hypertension; patients with white-coat hypertension are at low risk for adverse outcomes [15].

Nevertheless, it remains obscure whether patients with white-coat hypertension benefit from antihypertensive therapy because almost all hypertension trials have not admitted ambulatory BP measurement at baseline.

Even though the importance of ABPM is increasingly being acknowledged, several factors that are important to fully take advantage ABPM to better hypertensive patients' outcomes still remains unsolved. It is still not known whether treating patients with normal clinic BP and elevated ambulatory BP, which is popularly referred as masked hypertension, decreases risk for CVD and renal disease. Similarly, it is unknown whether withholding therapy for patients with elevated clinic BP and normal ambulatory BP (white-coat hypertension) is safe. In addition, in patients with elevated clinic and ambulatory BP, it is unknown whether a treatment strategy targeting ambulatory BP reduces adverse outcomes compared with a conventional strategy targeting clinic BP. In the background of such uncertainties, it remains important to determine whether intensive clinic-based hypertension treatment brings down nighttime systolic BP, daytime systolic BP, and 24-hour systolic BP.

The results of the SPRINT study had established the fact that intensive clinic-based hypertension treatment brings down nighttime systolic BP, daytime systolic BP, and 24-hour systolic BP as compared to standard clinic based hypertension treatment. The difference in ambulatory BP between groups was less than the difference measured by clinic BP. The study had further revealed that there was no significant difference in diurnal change in BP between groups. Furthermore, the SPRINT ambulatory BP ancillary study results are coherent with previous reports, suggesting that interventions targeting clinic BP bring down clinic BP more than 24-hour ambulatory BP and daytime ambulatory BP more than nighttime ambulatory BP. Earlier Elser and associates had demonstrated in the Symplicity HTN-2 Trial, renal sympathetic denervation to reduce in clinic systolic BP by 32 mm Hg at 6 months, but only an 11 mm Hg decrease in 24-hour ambulatory systolic BP [16].

In the same line, Zeymer and colleagues had reported 1-Year outcome results of observational study, the prospective 3A registry in which hypertension management of 13,000 outpatients under practice conditions. They demonstrated that clinic systolic BP decreased by 19 mm Hg 1 year after antihypertensive intensification, whereas 24-hour ambulatory systolic BP decreased by only 10 mm Hg.[17]It is noteworthy that all the study results mentioned above are based on baseline (pre-treatment) and follow-up (post-treatment) clinic and ambulatory BP measurements in observational studies and non-treat to target randomized trials. To demonstrate the same, Sierra *et al*. aimed to characterize 24-hour blood pressure (BP) values and categories inpatients with inclusion/exclusion criteria as that of the SPRINT trial from the Spanish ABPMRegistry. The investigators chose patients older than 50 years, with clinic systolic BP above 130mmHg and at high cardiovascular risk, but without diabetes, previous stroke or symptomatic heart failure. Ambulatory BP values were compared among various BP categories. A total of 39132 patients (34%) fulfilled the inclusion criteria of SPRINT trial. Ambulatory systolic BP was found to be substantially lower than office BP, with 42% of patients having daytime values below 130 mmHg, and 21% with 24-hour values below 120 mmHg. The authors' concluded that more than one-third of the hypertensive population included in the Spanish ABPMRegistry can be considered as SPRINT candidates, although one out of five has values of 24-hour systolic BP below 120 mmHg. These data thereby propose that cognition of ABP Mvalues could be helpful when planning treatment intensification in subset of high-risk patients [18].

On the contrary, the landmark HOT trial had also measured ambulatory BP in a sub-study; however, it demonstrated no difference in 24-hour ambulatory diastolic or systolic BP between randomized diastolic BP groups. One of the limiting factors is that the sample size for the HOT ambulatory BP sub-study was not adequately powered, and there were only

small differences in clinic BP between the treatment arms [11]. Taking into considerations all the above mentioned points, we can conclude that the SPRINT ambulatory BP results, therefore, represent the best demonstration of the effect of intensive clinic BP lowering therapy on ambulatory BP therefore, represent the best demonstration of the impact of intensive clinic BP lowering therapy on ambulatory BP [12].

To corroborate, the SPRINT study has various important implications in clinical practice. Firstly, the study results affirms that there was a significant BP difference between the intensive-treatment and standard-treatment groups using an independent technique of measuring BP. Secondly, SPRINT also achieved a significant difference in nighttime and daytime systolic BP. Results were uniform across most subgroups, though the difference in ambulatory BP between the treatment groups was particularly lower among subgroup of participants with chronic kidney disease, those 75 years of age or older, and females. ABPM was found to be more beneficial in patients with these characteristics, given the smaller impact of intensive treatment on ambulatory BP, which may increase the likelihood of lack of agreement between clinic and ambulatory BPs. It is concerning to note that clinic systolic BP was 6.85 mm Hg lower than the daytime ambulatory systolic BP in the intensive-treatment group, compared with 3.30 mm Hg lower in the standard-treatment group. This unique finding hints that ABPM may be more important when enforcing intensive clinic-based hypertension therapy to assess for higher BP outside the office compared with the clinical setting. This profile of BP, usually cited to as masked hypertension, is associated with increased risk of adverse outcomes attributed to HTN [5-9].

In SPRINT, intensive lowering of clinic BP had resulted in significant reductions in ambulatory BP, cardiovascular events, and all-cause mortality [9]. Hence, at least, SPRINT results circuitously hints that reductions in ambulatory BP are associated with improved clinical outcomes. The reduction in cardiovascular events and all-cause mortality may be partly due to the reduction in nighttime BP and BP variability observed with intensive lowering of clinic BP. The reduction in BP variability may be because of the lower clinic BP target or the increased use of antihypertensive drugs linked with lower BP variability such as chlorthalidone and calcium channel blockers [19]. The effect of the intensive clinic BP target on ambulatory BP may also be due in part to increased utilization of these long-acting medications. Surprisingly, there was no difference in the diurnal change in BP between treatment groups. Recently conducted studies suggest that nighttime hypertension itself, rather than diurnal change in BP, is associated with adverse outcomes [20, 21].

It is noteworthy; that clinic BP was lower than daytime ambulatory BP in SPRINT. This could be because of the careful guideline-based measurement of clinic BP in SPRINT, use of anautomated device, and a lower white-coat effect because participantswere coming to a known environment and staff and were allowed to rest alone for 5 minutes before BP measurement [22]. The SPRINT results reinforce the concept that ambulatory BP is required to assess the burden of hypertension during the course of patients' usual activities in their environment and cannot be reliably estimated by clinic BP readings. Finally, although the SPRINT investigators measured BP outside the research setting with ABPM, the BP achieved in the routine clinic setting remains unknown. Given that BP is not measured per American Heart Association recommendations in most clinics, understanding the achieved BP in the routine clinic setting during the treat to target phase is critically important to implementing SPRINT results.

An important issue that the SPRINT data couldn't address has to do with the evening dosing of antihypertensive medications, which has been shown to reduce nighttime BP and risk for CVD [23, 24]. Even though nighttime BP was lower in the intensive-treatment group and a higher percentage of intensive-treatment versus standard-treatment participants took antihypertensive medication in the evening (39% versus 31%), the effect of evening dosing with either intensive or standard clinic-based BP targets was not evaluated. Therefore, further studies are needed to measure whether targeting hypertension therapy based on ambulatory BP decreases adverse outcomes compared with clinic-based therapy, and whether evening dosing of antihypertensive therapy reduces the risk for CVD.

Conclusion

As demonstrated in the SPRINT study, the effect of intensive and standard clinic-based systolic BP targets on ambulatory BP. Compared with standard treatment, intensive treatment of clinic BP resulted in lower nighttime, daytime, and 24-hourambulatory BP, as well as BP variability but did not alter the diurnal BP pattern.

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