Night-time Chronotherapy with Diuretics: Effect on Sleep Quality and Duration in Patients with Hypertension in Lusaka, Zambia

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ABSTRACT

Background: Poor sleep plays an important role in the prevalence of hypertension. It increases the prevalence rate to 60%. The night-time dosing of blood pressure-lowering drugs has yielded positive results. Scholars have rarely investigated the relationship between night-time dosing of diuretics and the quality of sleep. The study aimed at evaluating quality and duration of sleep while on night-time dosing of diuretics and determine the commonly used blood pressure-lowering medication at University Teaching Hospital.

Materials and Methods: The study was a Prospective Cohort Study with 12 weeks follow-up. The sample consisted of 46 patients with hypertension, and on a diuretic, 25 of whom were taking their medication in the evening at 10 PM (study group), and 18 were in the 10 AM dosing schedule as a control.

Results: Overall, 43 were included in the analysis. Baseline and follow-up at 2, 8 and 12 Sleep quality and duration, and blood pressure level were available for 43 (93.5%) individuals. The study recruited more women (76.1%), and the majority were on hydrochlorothiazide and amiloride combination (65.2%). The 10 PM dosing showed better in quality of sleep and duration, and blood pressure-lowering as the follow-up continued with a p-value of less than 0.05 for Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), and for the blood pressure-lowering at 12 weeks.

Conclusions: The study showed beneficial effects of 10 PM dosing of diuretics in hypertensive patients, and the diuretic effect does not affect the quality and duration of sleep. Further, 10 PM dosing lowers the blood pressure significantly compared with 10 AM.

Keywords: chronotherapy, hypertension, quality of sleep, and sleepiness.

INTRODUCTION

Hypertension is characterised by systolic blood pressure equal to or above 140 mm Hg or diastolic blood pressure equal to or above 90 mm Hg[1, 2]. Various strategies have been put in place to manage hypertension, such as administering the drugs at bedtime. Theoretically, diuretics will cause lack of sleep if administered at bedtime, affecting sleep. Studies have been done to show the benefits of night time doing but never compare it to sleep quality. Quality sleep was defined by PSQI score of <5[3], and an ESS score of 0-6, respectively[4]. In the Sleep Heart Health Study done in America, subjects sleeping <5 hours per night had a higher frequency of prevalent hypertension, 60%[5]. Worldwide, hypertension accounts for approximately 20% of the world's adults; that is Blood Pressure higher than 140/90 mm Hg[1]. The prevalence increases with age as patients older than 60 years; the prevalence reaches to 50%[6].

From the understanding of the circadian rhythm of blood pressure, several studies have been done to utilise the night dose chronotherapy as the blood pressure surges in the early morning. The blood pressure tends to go up at 4 AM until 12 PM and then drops, reaching the lowest around midnight[7, 8,9 and 10].

The study by Hermida et al had shown that chronotherapy provides a means of individualising treatment of hypertension according to the circadian profile of blood pressure of each patient. This was referred to as a chronotherapeutic strategy which was a new option to optimise blood-pressure control and reduce risk. Nocturnal hypertension had increased risk of cardiac and cerebrovascular events because of the loss or reversal by 10 – 20% sleep-time blood pressure decline[7, 8].

The significant administration-time differences in the kinetics (i.e. chronokinetics) plus the beneficial and adverse effects (termed chromodynamics) of antihypertensive drugs were usually known. Therefore, bedtime and not morning time, dosing significantly reduced nocturnal blood pressure by Clonidine. Furthermore, valsartan administration

at bedtime instead of upon awakening results in improved diurnal/nocturnal blood pressure ratio. The dosing time of valsartan could be chosen in relation to any given patient's dipper status to improve therapeutic benefit and reduce cardiovascular risk[8].

Basil *et al* (2012) showed that African patients with hypertension treated with diuretics as monotherapy recorded an improvement in Blood Pressure levels, Left Ventricular Wall Dimension, Left Ventricular Mass and diastolic function which were amplified by night-time chronotherapy. Furthermore, they reported numerous benefits for better blood control with night-time chronotherapy such as normalising an abnormal dipping pattern as non-dipping was related to increased target organ damage, correction of an abnormal pattern spares end organs like the left ventricle and the kidneys from damage[11].

In Zambia and patients with African origin, the first-line treatment of hypertension was a diuretic, calcium channel blocker or angiotensin-converting enzyme inhibitors[12, 13, and 14]. The diuretics had shown benefits in patients of African origin as the first line in hypertension treatment[14]. They also had value in many of the disorders like heart failure that afflict the elderly, though they are more likely to cause side effects in all age groups[15,16]. However, most Physicians were reluctant to give diuretics in the evening because of the consequent diuresis, which may disturb sleep. However, we forget that diuresis as the basis of BP reduction with diuretics was an acute phenomenon in the first two weeks of therapy. Thereafter, a vasodilatory effect was operational[17].

Adequate sleep at night was essential for good health as sleepiness during the day could be an antecedent to falls, declining quality of life, and less functional recovery in older adults. Also, sleepiness during the day might also indicate that hypertension and diabetes were not well controlled. Over 50 years, habitual sleep duration has generally decreased in America, as 30% of Americans reported sleeping less than six hours per night [18, 19].

There have been no studies evaluating the troublesome nocturnal diuresis and sleep quality among the night-time group on diuretics. Our study aimed to evaluate the quality and duration of sleep while on night-time dosing of diuretics and determine the commonly used blood pressure-lowering medication used.

MATERIALS AND METHODS

The study was conducted from February 2015 to June 2015 in the Department of Internal Medicine of University Teaching Hospital, Clinic 5. Our study included 46 patients, and 43 finished the study. The patients included both naïve and experienced hypertensive on diuretics but not pregnant and not with severe hypertension. The control group consisted of 10 AM dosing and had 18 patients, while the study group consisted of 10 PM dosing and had 25 patients, and three were lost. All participants were surveyed on age, sex, and type of diuretic, blood pressure, the sleep quality and sleepiness on each visit. The participants were followed at 2, 8 and 12 weeks. The study protocols were conducted in accordance with ERES Converge Ethics committee, Ref No.2014. Sept.008 and clearance from University Teaching Hospital management.

Measurement of age, blood pressure, sleeps quality and sleepiness.

The age was measured in years, and blood pressure in mmHg and the sleep quality and sleepiness as a score. The measurements were repeated at 2, 8 and 12 weeks and computed for each participant.

Definitions

Chronotherapy was the treatment of an illness or disorder by administering a drug at a time of day believed to be in harmony with the body's natural rhythms. Hypertension was defined as blood pressure greater or equal to140/90mmHg. Sleep quality was PQSI scored as; total < 5 associated with good sleep quality and total > 5 associated with poor sleep quality. The sleepiness was scored by ESS as the sum of 10 or more from the eight individual scores reflecting above normal daytime sleepiness and need for further evaluation.

Statistical Analysis

The data was analysed using SPSS version 22; Participants' characteristics were presented as means, or percentages for the continuous variables. Chi-square test for categorical variables with statistical significance set at $p < 0.05$ was performed.

RESULTS

Baseline Characteristics

Our study included 43 eligible individuals for analysis, with 18 in the 10 AM group (41.8%), while we had 25 10 PM group (58.2%). The females were more than male at 72%. At baseline

and 12 weeks' follow-up of sleep quality and duration, and BP readings were available for 43 (97% follow up) while three were lost. The age distribution in the groups showed that the median age of 54.5 years in AM group and a median of 59 years in the PM group. The age range was 36 to 69 years in the AM and 35 to 75 years in the PM.

Clinical Outcomes:

(a) Quality of sleep as measured by PSQI

From the baseline, sleep score by using PSQI was poor; both groups had a poor sleep as most of the participants scored more than 5. However, as the follow up continued, the 10 PM dosing group had improved quality of sleep. From our study findings, there were significant differences in quality of sleep at 2, 6 and 12 weeks follow up a with a p-value of less than 0.05 at 12th week.

(b) Duration of sleep as measured by ESS.

For each point visit, the duration of sleep was analysed and presented. The trend showed adequate sleep in the 10 PM as the follow continued though with less significant differences with p values greater than 0.05 from enrolment to 12 weeks follow up.

(c) The blood pressure control in the 10 AM and 10 PM dosing times.

At baseline, the blood pressure readings showed minor differences in the blood pressure control between the lowest and highest in the two groups. However, there was a reduction in the 10 PM dosing group with significant differences at 12 weeks follow up, with the p-value of less than 0.05.

(d) To determine the commonly used diuretic for hypertension.

Of all the 43 participants with hypertension, 16 (51.6%) in AM and 15(48.4%) in PM were on HCTZ with Amiloride drug combination though it was of less significance.

DISCUSSIONS:

Scholars have utilised chronotherapy to individualise treatment of hypertension according to the circadian profile of blood pressure of each patient. The chronotherapeutic strategy provides a new option to optimise blood-pressure control and to reduce risk. Nocturnal hypertension had increased risk of cardiac and cerebrovascular events because of the loss or reversal by 10 – 20% sleep-time blood pressure decline[7, 8].

Our study showed a higher percentage of women participants than men, explaining a higher prevalence of hypertension in women, 72% that was observed. This was contrary to the study done by Goma and colleagues, which reported that the prevalence was high in men[20]. However, it was observed that women were more willing to participate than male counterparts in our study.

Our study showed a trend at baseline as most participants had a PQSI score of more than 5 in both groups. However, there was a significant improvement in sleep quality at 12 weeks in the 10 PM group with time. In the Sleep Heart Health study, though not concentrating on patients on diuretics, it showed the prevalence of hypertension worsens to 60% in patients with poor sleep, sleeping less than 5 hours in a night[5, 18, 19].

The study showed that the blood pressure reduction was significant in the night-time dosing of diuretic at the end of follow-up. This is in line with a study done by Chikao *et al*, where it was observed that despite the high Body Mass Index (BMI) in poorly controlled hypertensive patients, the BP reduction was well reduced with night-time dosing of losartan/HCTZ combination [21, 22,23].

Despite our study using clinic BP monitoring as compared to ABPM. The BP follow-up at 12 weeks showed much reduction with a p-value of less than 0.05. This was a general practice as reported by Portaluppi *et al* that the practitioners in the BP monitoring rely on cuff BP in the day time. They concluded that target organ damage was more closely associated with Ambulatory Blood Pressure Monitoring (ABPM) than with clinic BP. Some specific features of the 24-h BP pattern were linked to the progressive injury of target tissues and triggering of cardiac and cerebrovascular events. In particular, the extent of the sleep BP decline is deterministic of cardiovascular injury and risk[24, 25].

In contrast to Basil et al[11], our study looked at the BP control, quality and duration of sleep and showed a positive outcome in the night-time dosing (study group) compared to the control group. Basil *et al* 2012 findings encouraged the use of diuretics in the evening. There were numerous benefits for better blood control with night-time chronotherapy. It normalises an abnormal dipping pattern, and because non-dipping is related to increased target organ damage, correction of an abnormal pattern spares end organs like the left ventricle and the kidneys from damage. Following the limitation from Basil *et al*[11] study, they did not

look at troublesome nocturnal diuresis and quality of sleep among the night-time group[11]. This further clears physicians' fear to prescribe the diuretic to be dosed in the evening as reported by Sica[17].
The observation in our study was that as the follow up continued; the participants provided the same answers as the previous visit. This was in contrast with Wrzus *et al* who concluded that subjective and objective assessment of the quality of sleep yielding similar results[26].

Most of the participants were on HCTZ with Amirolide combination type of diuretic. This could be attributed to the fact that the combination was part of the essential drug list in Zambia and first line for hypertension in patients with African origin[12, 14].

CONCLUSION

There were benefits in taking diuretics in the night time as the quality and duration of sleep was not affected amongst the hypertensive patients with night-time chronotherapy of diuretics. Therefore, we can safely recommend the night time administration as the blood pressure-lowering effect was more pronounced than the morning administration. It was further observed that the type of diuretic does not have a significant difference, they were equally effective, and the quality and duration of sleep were unaffected by the diuretic type.

The strengths of our study included its random recruitment and completeness of follow-up. The cohort study was an ideal design for interventional research when, as here, there were several outcomes of interest. We believe that PSQI and ESS tools were the most appropriate measure of sleep quality and duration in the resource-limited situation.

The limitations of our study were Irregular availability of HCTZ-amiloride at the study site during the time, which could have affected adherence to treatment in both arms. There were also limited financial resources to procure ambulatory accelerometers for an objective measure of quality and duration of sleep and Ambulatory Blood Pressure Monitoring machines. There was also co-administration of other antihypertensive medicines which could have affected our outcomes.

ACKNOWLEDGEMENTS

We thank Mukosha Moses (University of Zambia) for the guidance. We also thank Dr Basil O.N (Nigeria) for his article on Diuretics in Medscape.

REFERENCES:

1. World Health Organisation (2013). World Health Day Report: A global brief on hypertension; silent killer, a global public health crisis.
2. JNC VII guidelines, 2013.
3. Pittsburgh Sleep Quality Index - Sleep Quality Assessment Tool.
4. The Epworth Sleepiness Scale
5. Gottlieb DJ, Redline S, Nieto FJ. Association of usual sleep duration with hypertension: the Sleep Heart Health Study Sleep. 2006; 29 (8): 1009 - 1014.
6. Albert WD. Epidemiology of Hypertension. Drug and Diseases update. 2013 www.medscape.com (February, 2014)
7. Hermida RC, Smolensky M. Chronotherapy of hypertension. Current Opinion Nephrology Hypertension 2004; 13: 501–550.
8. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC Study. Chronobiology. International. 2010: 27: 1629–1651.
9. Kario K, Schwartz JE, Pickering TG. Changes in nocturnal blood pressure dipping status in hypertensives by night-time dosing of alpha-adrenergic blocker, doxazosin; results from the HALT study. Hypertension 2000; 35: 787–794.
10. Neutel JM, Smith DH. The circadian pattern of blood pressure: cardiovascular risk and therapeutic opportunities. Current Opinion Nephrology Hypertension.1997; 6(3):250-6.
11. Basil NO, Esther NO, Jayne NAA. Diuretic Drugs Benefit Patients with Hypertension More with Night-time Dosing. Therapeutic Advances in Drug Safe; 2012; 3(6):273-278.
12. Ministry of Health, Zambia National Formulary Committee. Standard Treatment Guidelines, Essential Medicines List, Essential Laboratory Supplies for Zambia. 3rd edition, 2013. Lusaka, Zambia.
13. Ferdinand K, Ferdinand D. Race-based therapy for hypertension. Possible benefits and potential netfalls. Expert Review Cardiovascular Therapy. 2008; 6: 1357–1366.
14. Gombert T, Steichen O, Plonin P. Hypertensive disease in subjects born in Sub-Sahara Africa or in Europe referred to a hypertension unit. A cross-sectional study. Bull Academy of Natural Medicine. 2007; 191: 1745–1754, discussion 1754–1755.

16. McLennan WJ. Diuretics in elderly: how safe? British Medical Journal 1988; 19(296) no 6636 page 1551.
17. Khurship F, Aqil M, Alam MS, Kapur P,Pillai KK. Monitoring of adverse drug reactions associated with antihypertensive medicines at the University Teaching Hospital in New Delhi. DARU Journal of Pharmaceutical Sciences. 2012; 20:34
18. Sica D. Thiazide and loop diuretics. Clinical Cornerstone 2008; 4: 439–442.
19. National Center for Health Statistics. Quick Statistics: Percentage of adults who reported an average of 6 hours of sleep per 24-hour period, by sex and age group - United States. 2005; 54(37): 933 .
20. Hoevenaar-Blom MP, Spijkerman AMW, Kromhout D, Van den Berg JF, Verschuren WMM. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN Study. SLEEP; 2011; 34(11):1487-1492.
21. Goma FM, Nzala SH, Olusegun B, Songolo P, Zyaambo C, Rudatsikira E, et al. prevalence of hypertension and its correlates in Lusaka urban district of Zambia: a population-based survey. International Archives of Medicine. 2011; 4:34 doi:10.1186/1755-7682-4-34.
22. Chikao I, Yoshihiko S, Toshiaki O, Kyoichi M, The fixed-dose combination of Losartan/ HCTZ elicits potent BP lowering during night time in obese hypertensive patients. Journal of Clinical Medical Research. 2014; 6(1): 8–16.
23. Williams B, Lacouriccere Y, Schumacher H, Gosse P, Neutel JM. Antihypertensive efficacy of Telmisartan Vs Ramipril over the 24h dosing period, including the critical early morning hours: a pooled analysis of the PRISMA I and II randomised trial. Journal of Human Hypertension. 2009; 23, 610–619
24. Zeng J, Jia M, Ran H, Tang H, Zhang Y, Zhang J, et al. Fixed-combination of amlodipine and diuretic chronotherapy in the treatment of essential hypertension: improved blood pressure control with bedtime dosing-a multicenter, open-label randomised study. Hypertension Research. 2011; 34(6):767-72.
25. Portaluppi F, Michael HZ, Smolensky MH. Perspectives on the chronotherapy of hypertension based on results of MAPEC study. Chronobiology International. 2010; 27(8): 1652–1667.
26. Thomas M, Sakir U, Peter B. Management of Hypertension with fixed-dose combination of Candesartan and HCTZ: Patient perspectives and clinical utility. Vascular Health and Risk Management. 2009; 5 1043–1058
27. Wrzus C, Brandmaier AM, Von Oertzen T, Mu ¨ller V, Wagner GG. A New Approach for Assessing Sleep Duration and Postures from Ambulatory Accelerometry. PLoS ONE. 2012; 7(10): e48089. doi:10.1371/journal. pone.0048089, (April, 2014).

TABLES

Table 1. Blood Pressure control

The tables show changes in blood pressure at baseline to 12 weeks' follow-up, comparing the Chi-square, N=43.

	AM		PM		P
	N	%	N	%	
Baseline					0.988
<140	8	50	8	50	
140-149/90-94	3	50	3	50	
150-159/95-99	11	52.4	10	47.6	
Weeks 2					0.681
<140/90	11	47.8	12	52.2	
140-149/90-94	8	57.1	6	42.9	
150-159/95-99	2	40	3	60	
>160/100	1	100	0	0	
Week 8					0.105
<140/90	14	42.4	19	57.6	
141-149/90-94	7	77.8	2	22.2	
>160/100	1	100	0	0	
Week 12					0.020
<140/90	17	44.7	21	55.3	
141-149/90-94	5	100	0	0	

Table 2: Quality of sleep by PSQI

The table shows comparisons of sleep quality and duration by using the SD from baseline to 12 weeks follow-up by using the PSQI scale.

	AM		PM		P
	N	**%**	**N**	**%**	
PSQI Baseline					0.092
<5	6	35.3	11	64.7	
>5	16	61.5	10	38.7	
PSQI 2 weeks					0.021
<5	8	34.8	11	64.7	
>5	14	61.5	10	18.7	
PSQI 8weeks					0.002
<5	14	40	21	60	
>5	8	100	0	0	
PSQI 12weeks					0.010
<5	16	34.8	21	56.8	
>5	6	100	0	0	

Table 3. **The measure of Sleepiness by ESS at enrolment and follow-up**

	AM		**PM**		**P**
	N	**%**	**N**	**%**	
Baseline					0.073
1-6	15	68.2	7	31.8	
7-8	4	33.3	8	66.7	
>9	3	33.3	6	66.7	
ESS 2 weeks					0.664
0	1	100	0	0	
1-6	15	46.9	17	53.1	
7-8	4	57.1	3	42.9	
>9	2	66.7	1	33.3	
ESS 8 weeks					0.215
0	1	100	0	0	
1-6	19	47.5	21	100	
7-8	2	100	0	0	
ESS 12 weeks					0.215
0	1	100	0	0	
1-6	19	47.5	21	52.5	
7-8	2	100	0	0	

FIGURES

Figure 1 Baseline Statistics

Description of Study Population According to Gender at enrolment (N = 43)

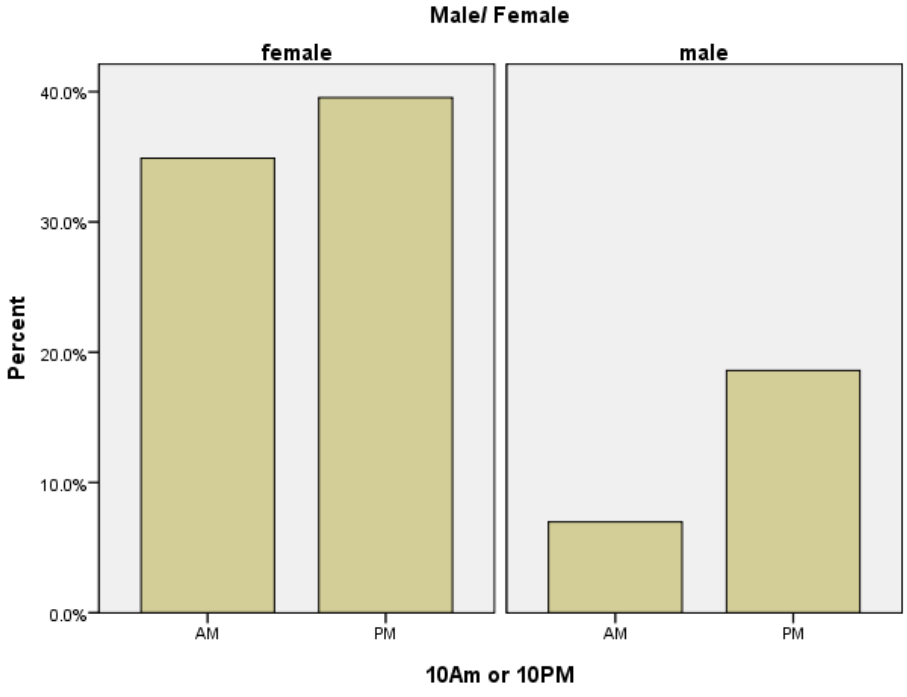
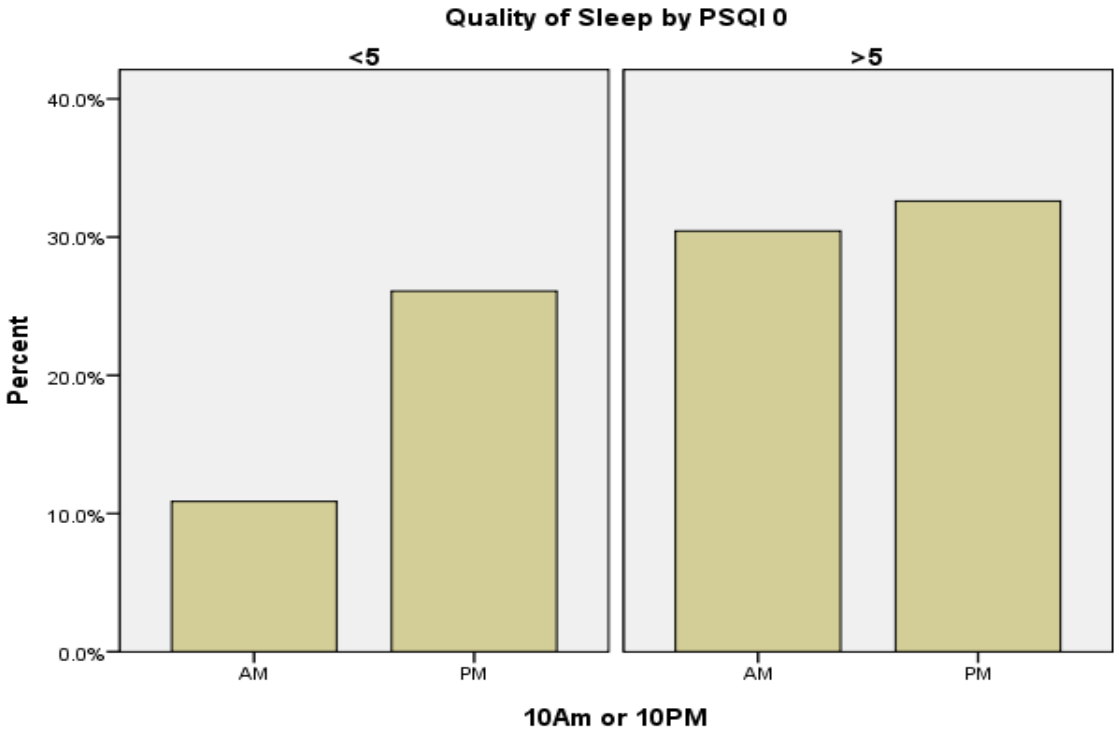


Figure 2. Quality of Sleep score comparison

The baseline sleep score using PSQI had a poor sleep as most of the participants scored more than five, and at 12 weeks of sleep quality where the 10 PM group performed better.



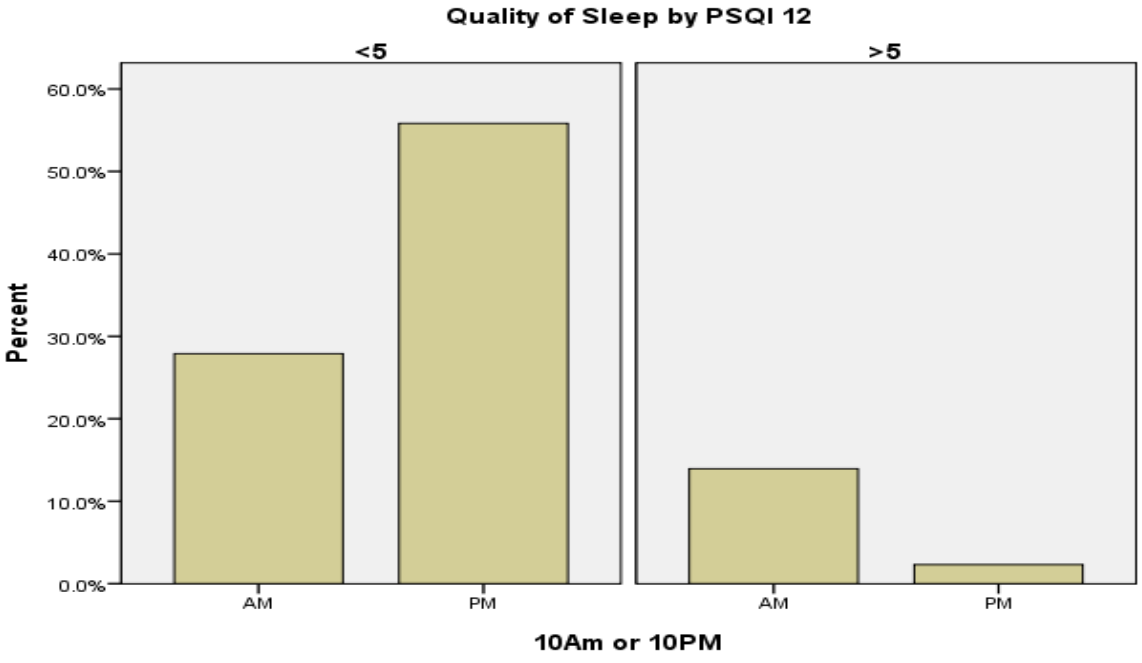


Figure 3. Blood Pressure comparison

The blood pressure readings at baseline and 12 weeks, showing differences in the blood pressure control between the lowest and highest.