THE EFFECT OF NIGHT-TIME DIURETIC CHRONOTHERAPY ON QUALITY AND DURATION OF SLEEPAMONG ZAMBIAN HYPERTENSIVE PATIENTS

By

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A dissertation submitted to the University of Zambia in partial fulfilment of the degree of Masters in Clinical Pharmacy.

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DECLARATION

I**, DAVID BANDA** hereby declare that the work on which this discussion is based is original, except were acknowledgement indicate otherwise

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CERTIFICATE OF APPROVAL

This dissertation of DAVID BANDA has been approved as partial fulfilment of the requirements for the award of the Degree of Masters of Clinical Pharmacy by the University of Zambia

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ABSTRACT

Poor sleep plays an important role in the prevalence of hypertension. It increases the prevalence rate to 60%. It is thought that sleep regulates stress hormones and helps nervous system. Overtime, lack of sleep hurt the body ability to regulate stress hormones, leading to high blood pressure. The night time dosing of blood pressure lowering drugs have 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.

Methods: The sample consisted of 43 patients with hypertension and on diuretic, 25 of whom were taking their medication in the evening at 10 PM and 18 were in the 10 AM dosing schedule. The BP was measured with cuff sphygmomanometer at enrolment and follow-ups. The quality of sleep was measured using the Pittsburgh Sleep Quality Index (PSQI) score while the duration of sleep was measured with Epworth Sleepiness Scale (ESS) score at enrolment and follow-ups. A PSQI score of less than 5 indicated good sleeps while an ESS score of 1-6 as a good duration of sleep.

Results: Overall, 43 were included in the analysis. The 10AM group had 18 (41.8%), while the 10PM group had 25 (58.2%) at enrolment. The study recruited more women (72.0%) and the majority were on hydrochlorothiazide and amiloride combination (72.0%). The 10PM dosing showed significant differences in quality of sleep with p-value of 0.010 at 12 weeks follow-up. The duration of sleep did not show significant differences between the groups with p-value of 0.215. The blood pressure lowering was significant in the 10PM group with p-value of 0.020 at 12 weeks follow-up. Conclusions: The study suggested that the 10PM dosing of diuretics in hypertensive patients and the diuretic effect does not affect the quality and duration of sleep. Further, 10PM dosing lowers the blood pressure significantly compared with 10AM.

DEDICATION

To my wife, Maggie and children. My late mother for her courage and dedication to school work.

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This study would have not been possible without support of many people. Many thanks to my supervisors; Dr LT Muungo and Dr N Lambwe for their guidance and support until sense was derived at all stages.

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TABLE OF CONTENT

Page

CHAPTER THREE

CHAPTER 4

4.0 RESULTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS:

ABPM	-	Ambulatory Blood Pressure Monitoring
ACEI	-	Angiotensin Converting Enzyme Inhibitor
ARB	-	Angiotensin Receptor Blocker
BMI	-	Body Mass Index
BP	-	Blood Pressure
CVD	-	Cardiovascular Diseases
ESS	-	Epworth Sleepiness Scale
HCTZ	-	Hydrochlorothiazide
JSH	-	Japanese Society of Hypertension
MAPEC	-	Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events
MoH	-	Ministry of Health
MORGEN	-	Monitoring Project on RISK Factors and Chronic Diseases in the Netherlands
PRISMA	-	Prospective, Randomised Investigation of Safety of Micardis Vs Ramipril Using ABPM
PSQI	-	Pittsburgh Sleep Quality Index
SD or Std Dev	-	Standard Deviation
UNZA	-	University of Zambia
UTH	-	University Teaching Hospital
WHO	-	World Health Organization

OPERATIONAL DEFINITIONS:

In this research proposal project the following terms will be interpreted as follows;

Chronodynamics.

The effects of drugs are modified based on the time at which they are administered.

Chronotherapy.

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.

Chronopharmacokinetics.

The study of the temporal changes in absorption, distribution, metabolism and elimination and thus takes into account the influence of time of administration on these different steps.

Circadian Rhythm.

Any biological process that displays an endogenous, entrainable oscillation of about 24 hours.

Diuretics.

Single or in combination of Thiazides, Loop and Potassium sparing.

Hypertension.

Systolic blood pressure equal to or above 140mmHg and/or diastolic blood pressure equal to or above 90mmHg.

Mild Hypertension.

Blood pressure systolic 140 - 149 mmHg and Diastolic blood pressure 90-94 mmHg.

Moderate Hypertension

Blood pressure systolic equal 150-159 mmHg and Diastolic blood pressure 95-99 mmHg.

Severe Hypertension.

Blood pressure systolic equal to or above 160 mmHg and Diastolic blood pressure equal to or above 100 mmHg.

CHAPTER ONE

1.0 Introduction.

1.1 Background:

Hypertension is characterised by systolic blood pressure equal to or above 140 mm Hg and/or diastolic blood pressure equal to or above 90 mm Hg (WHO, 2013 report). Quality sleep is defined by Pittsburgh Sleep Quality Index (PSQI) score of <5 and Epworth Sleepiness Scale ESS score of 0-6. It is thought that sleep regulates stress hormones and helps nervous system. Overtime, lack of sleep hurt the body ability to regulate stress hormones, leading to high blood pressure. Therefore, there is high prevalence of hypertension in people with poor sleep as reported in the Sleep Heart Health Study done in America, where subjects sleeping <5 hours per night had a higher frequency of prevalent hypertension of up to 60% (Gottlieb et al., 2006).

Worldwide, hypertension was accounting for approximately 20% of the world's adults with hypertension; that is Blood Pressure in excess of 140/90 mm Hg. The prevalence of hypertension also increases with age, as patients older than 60 years, the prevalence reaches to 50% (Albert, 2013).

From the understanding of 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 surge at 4 AM until 12 PM and then drops reaching the lowest around midnight (Hermida and Smolensky, 2004).

Further, Hermida *et al*, (2004) had shown that chronotherapy provides a means of individualizing treatment of hypertension according to the circadian profile of blood pressure of each patient. This constituted chronotherapeutic strategy as a new option to optimize blood-pressure control and to reduce risk. The nocturnal hypertension had increased risk of cardiac and cerebrovascular events because of the loss or reversal by 10 – 20% sleep-time blood pressure decline (Hermida and Smolensky, 2004).

There were significant administration-time differences in the kinetics (i.e. chronokinetics) plus the beneficial and adverse effects (termed chronodynamics) of antihypertensive drugs which were usually known. Therefore, bedtime and not

morning time, dosing significantly reduced nocturnal blood pressure by Clonidine (Hermida and Smolensky, 2004). Furthermore, valsartan administration at bedtime as opposed to upon awakening results in improved diurnal/nocturnal blood pressure ratio, such that the dosing time of valsartan could be chosen in relation to the dipper status of any given patient to improve therapeutic benefit and reduce cardiovascular risk (Hermida and Smolensky, 2004)

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 normalizing 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 (Basil *et al*., 2012).

In Zambia, the first line treatment of hypertension is a diuretic, calcium channel blocker or angiotensin converting enzyme inhibitors (Ministry of Health, 2013).

The diuretics had varied spectrum of electrolyte disorders especially on sodium and potassium which were risk factors for adverse outcomes of fall and fractures affecting quality of life (Arampatzis *et al.*, 2013). With diuresis as an effect at night, sleep would be affected hence the reluctance by health workers to give at night (Sica, 2008). Sleep at night was essential for good health. Sleepiness during the day could be an antecedent to falls, declining quality of life, and less functional recovery in older adults. Sleepiness during the day might also be an indicator that hypertension and diabetes are not well controlled. Habitual sleep duration over the past 50 years generally has decreased in America as 30% of Americans reported sleeping less than 6 h per night (National Centre for Health Statistics, 2005).

Further, there have been few studies evaluating the troublesome nocturnal diuresis and quality of sleep among the night-time group on diuretics. This 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 used.

1.2 RATIONALE OF STUDY

Subjects sleeping <5 hours per night had a higher frequency of prevalent hypertension (Gottlieb *et al.*, 2006). There was also growing body of knowledge on the night time chronotherapy in hypertension management including the use of diuretics (Hermida and Smolensky, 2004). However, the studies so far concentrated on the Blood Pressure control outcomes. The studies involving diuretics also ignored the troublesome nocturnal diuresis, consequently the quality and duration of sleep of the patient.

The problem is also compounded by the negative perspectives by both health workers and patients due to inadequate evidence on the quality and duration of sleep with night-time chronotherapy with diuretics.

Through this study on the quality and duration of sleep with night-time chronotherapy of diuretics, evidence was generated on night time chronotherapy of diuretics in hypertension. This study would further add some insights in relation to diuretic night time chronotherapy.

1.3 RESEARCH QUESTIONS.

1.3.1 Does night-time diuretic chronotherapy affect quality and duration of sleep among hypertensive patients?

1.4 SIGNIFICANCE OF STUDY.

Following the limitation from Basil et al study, where they did not look at troublesome nocturnal diuresis and quality of sleep among the night-time group (Basil et al., 2012).

Good sleep at night is essential for good health. As sleepiness during the day could be an antecedent to declining quality of life, and less functional recovery in older adults who are also at risk to hypertension. Sleepiness during the day might also be an indicator that hypertension and diabetes were not well controlled.

Further, the Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events (MAPEC) study recommended that if there were more than one antihypertensive, one should be given at bed time (Hermida *et al.,* 2010).

However, it did not specify the group of drugs recommended to be given in the evening.

The findings of the study are useful to the patients for optimization of treatment with diuretics with new evidence from the study.

1.5 GENERL OBJECTIVE.

To compare quality and duration of sleep in hypertensive patients on diuretic therapy with 10 AM and 10 PM dosing times.

1.6 SPECIFIC OBJECTIVES.

1.6.1 To determine the quality and duration of sleep differences in the 10 AM and 10 PM timing of the dose of diuretic.

1.6.2 To determine the blood pressure control with difference in the 10 AM and 10 PM dosing times.

1.6.3 To determine the commonly used diuretic for hypertension.

CHAPTER TWO

2.0 LITERATURE REVIEW.

The Literature Review describes the burden of hypertension, the night dosing and use of diuretics, and assessment of quality and duration of sleep.

Worldwide, hypertension accounts for approximately 20% of the world's adults; that is Blood Pressure in excess of 140/90 mm Hg. The prevalence increases with age. In patients older than 60 years, the prevalence reaches 50% (Albert, 2013). Despite Sleep Heart Health study not concentrating on patients on diuretics, it showed the prevalence worsening to 60% in patients sleeping less than 5 hours in a night (Gottlieb et al., 2006).

According to the World Health Organisation (WHO, 2013) cardiovascular disease accounts for approximately 17 million deaths a year globally. Hypertension as a complication, accounts for 9.4 million deaths worldwide every year. Of all the cardiovascular mortality, hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke. Of the total death due to cardiovascular, nearly 80% of deaths occur in low- and middle-income countries, where our country if is found (WHO, 2013).

A survey done in rural Zambia (Kaoma and Kasama) had revealed the average prevalence of hypertension was 28.05%, highest in Kasama (Mulenga *et al.*, 2013). The study concentrated on prevalence than the risk factors that were associated with Hypertension.

The prevalence rate is high in urban Lusaka at 34.8% with males on the higher side. This was reported highest as compared to South Africa, Eretria and Uganda on overall (Goma *et al.*, 2011). Despite looking at the risk factors, the study did not mention how they ruled out white coat hypertension.

In chronotherapeutic, the morning drug administration loose efficacy in the last few hours of the dosing interval, resulting in the early morning surge. Despite having the controlled onset and extended release delivery systems, the night dosing of these delivery system at night provide maximal effect as the drug concentrations reach maximum level between 0600 h and 1200 h when the blood pressure is rising at its

greatest rate thereby reducing the cardiovascular accidents (Neutem and Smith, 1997).

Recent studies have shown that chronotherapy provides a means of individualizing treatment of hypertension according to the circadian profile of blood pressure of each patient. This constitutes chronotherapeutic strategy as a new option to optimize blood-pressure control and to reduce risk. The nocturnal hypertension has increased risk of blood pressure decline (Hermida and Smolensky, 2004).

There are significant administration-time differences in the kinetics (i.e. chronokinetics) plus the beneficial and adverse effects (termed chronodynamics) of antihypertensive drugs which are usually known. Therefore, bedtime and not morning time, dosing significantly reduces nocturnal blood pressure by Clonidine. Also, valsartan administration at bedtime as opposed to upon awakening results in improved diurnal/nocturnal blood pressure ratio, such that the dosing time of valsartan can be chosen in relation to the dipper status of any given patient to improve therapeutic benefit and reduce cardiovascular risk (Hermida and Smolensky, 2004).

In a study done by Chikao, 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 (hydrochlorthiazide) combination (Chikao *et al.*, 2014). Despite the study having small sample size with no comparison, the benefits were seen in the night time chronotherapy.

Also the study with amlodipine complexes, the morning surge of Blood Pressure (BP) was reduced to a greater degree in the bed time group, the nocturnal BP and 24 h mean BP were lower and most patients converted from non-dipper to dipper BP. Therefore, the amlodipine complexes have different efficiencies depending on treatment time (Zeng *et al.*, 2011). The complexes contained amlodipine and hydrochlorothiazide, however, they did not report on the quality of sleep.

Francesco and Michael, (2010) observed that the general practice of practitioners in the BP monitoring that they rely on cuff BP in the day time. They recommended that a supplementary BP assessment at home be performed during different times of activity span to complement the clinic BP. Further, they concluded that (i) target

organ damage is more closely associated with Ambulatory Blood Pressure Monitoring (ABPM) than with clinic BP and (ii) some specific features of the 24-h BP pattern are linked to the progressive injury of target tissues and triggering of cardiac and cerebrovascular events. In particular, the extent of the asleep BP decline is deterministic of cardiovascular injury and risk (Portaluppi and Smolensky, 2010).

The results from the prospective Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events (MAPEC) study thus indicate that bedtime chronotherapy with ≥1 hypertension medications, compared to conventional upon-waking treatment with all medications, more effectively improves BP control, better decreases the prevalence of non-dipping and, most importantly, significantly reduces cardiovascular Diseases (CVD) morbidity and mortality (Hermida *et al.*, 2010).

In prospective, Randomised Investigation of Safety of Micardis (Losartan with Hydrochlorothiazide) Vs Ramipril Using ABPM I and II (PRISMA I and II) studies, the long acting Telmisartan proved superior with single dosing as compared to Ramipril suggesting the better quality of 24 h BP control and improved tolerability of the Angiotensin Receptor Blocker (ARB) as the most important difference with Angiotensin Converting Enzyme (ACE) inhibitors (Williams *et al.*, 2009).

The night time dosing with an alpha blocker doxazosin therapy reduced BP equally as a morning dosing. However, the night time also shifted the dipping status toward less nocturnal BP dipping. The effect was not only dependent on mechanism of action but also on time of administration. The night time dosing of doxazosin reduces the morning BP surge (Kairo *et al.*, 2000). The blunted diurnal BP variation is a strong predictor of death, in large part, because it is associated with other cardiovascular risk factors, but this may be accounted for, in large part, by its association with other cardiovascular risk factors. Therefore, non-dipping of heart rate and ambulatory heart rate level should be taken into account as a risk assessment in patients with hypertension in addition to ambulatory BP parameters in clinical practice (Brotman *et al.*, 2008).

It has also been reported that diuretics are also used as fixed dose combination with other antihypertensive. Thomas summarized that diuretics were used more frequently in elderly as a combination or alone hence the role of fixed dose combination (Thomas, 2009). Further, the diuretics had varied spectrum of electrolyte disorders

especially on sodium and potassium which were risk factors for adverse outcomes of fall and fractures affecting quality of life (Arampatzis *et al.*, 2013).

Basil *et al,* (2012) findings encouraged use of diuretics in the evening. There were numerous benefits for better blood control with night-time chronotherapy. It normalizes 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 (Basil *et al.,* 2012). Despite the duration and smaller sample size, they highlighted the insights on the night time dosing of diuretics.

Following the limitation from Basil *et al* study, they did not look at troublesome nocturnal diuresis and quality of sleep among the night-time group (Basil *et al.,* 2012). The quality of life should not be ignored in diuretic therapy to add more convincing reasons to night time dosing of diuretics.

However, most health workers are reluctant to give diuretics in the evening because of the consequent diuresis which may disturb sleep. However, diuresis as the basis of BP reduction with diuretics is an acute phenomenon that occurs in the first 2 weeks of therapy. Thereafter, a vasodilatory effect is operational (Sica, 2008).

The statistics show that Sub-Saharan Africans were more frequently given antihypertensive medication than their paired controls (84 vs 74%, $p<0.001$), and their antihypertensive regimens were more likely to include a diuretic (54 vs 46%, $p=0.001$) for obvious reason that African origin hypertensive patients respond well to diuretics (Gombet *et al.,* 2007). The evidence on efficacy and safety comparisons and cardiovascular outcomes recommend thiazide diuretics and/or long-acting calcium channel blockers as initial treatment for Blacks (Ferdinand and Ferdinand, 2008).

Apart from the diuresis, diuretics also cause hyponatremia, weakness, confusion, postural hypotension, falls, fits, gout, hypokalemia and deafness which can affect the quality of life. .An assessment of the antihypertensives, diuretics were second causing side effects after calcium channel blockers. The diuretics caused fatigue, visiual impairment dizziness and loss of appetite (Khurshid et al., 2012). However, the diuretics used were not representative of the diuretics found in Zambia.

The quality of life questionnaire covers symptomatic (physical) well-being, psychological well-being and perception of the effects of antihypertensive treatment on lifestyle. They are considered to be the three areas most important to the hypertensive patient (Bulpitt and Fletcher, 1990).

There are subjective and objective way of assessing quality and duration of sleep, and most studies have recommended the objective way as the most reliable. However, ambulatory accelerometry yielded results that were similar to subjective reports of sleep duration and quality (Wrzus *et al.,* 2012).

Most of the assessments have neglected the lifestyle behaviours like sleep habits, contrary to the recommendations of the Japanese Society of Hypertension (JSH) (JSH, 2014) mostly the assessment are on safety, efficacy and cost.

However, the Monitoring Project on Risk Factors and Chronic Diseases in the Netherlands (MORGEN) study concluded that short duration of sleep and poor sleep was associated with total cardiovascular disease and Coronary Heart disease incidence (Hoevenaar-Blom *et al.*, 2011).

The study using Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) concluded that subjective sleep disturbances were associated with risk of fall in older men, independent of confounders (Katie *et al.*, 2014).

In summary, it can be seen that the prevalence of hypertension is high especially in the developing countries. The recommended choice of drugs was the diuretics particularly in the black Africans race. Recently, studies have reported growing benefits of night time administration of antihypertensive drugs including diuretics. In most of the studies reviewed, night time quality of life or sleep was not addressed in relation to the use of the antihypertensives at night.

CHAPTER THREE

3.0 METHODOLOGY:

3.1 Study Design:

This was a cohort study for the period of 12 weeks involving patients with hypertension. The study was conducted from February 2015 to June 2015 in the Department of Internal Medicine of University Teaching Hospital, Clinic 5. The patients were enrolled into morning (10AM) and night-time (10PM) ingestion groups. The patients were assessed at enrolment, 2, 8 and 12 week interval after enrolment. The patients were asked to come back for follow ups.

On a daily basis, the Hypertensive patients were arranged alphabetically and numbered. The spot BP checks were done by the nurse before seeing the physician. Thereafter, those with odd numbers were enrolled in 10 AM and those with even numbers were in 10PM. On exit to pharmacy, the patients were interviewed using the questionnaire on the sleep quality and duration. The dosing frequency remained as it was prescribed and the only modification was the timing in the day.

Information on sleep quality and duration was obtained by self-administered questionnaire extracted from Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS).

The participants were categorised as 10 AM dosing as unexposed and 10 PM dosing as exposed group.

3.2 Target Population.

Hypertensive patients in Lusaka district at the time of study.

3.3 Study population.

Hypertensive patients enrolled at University Teaching Hospital in internal medicine in Lusaka at clinic 5 and prescribed diuretics.

3.4 Study site:

The study was conducted at the University Teaching Hospital in Lusaka, Zambia in Internal Medicine, at Clinic 5.

3.5 Inclusion criteria:

- Mild to Moderate hypertension
- Taking at least one diuretic

3.6 Exclusion criteria:

- Severe hypertension
- Current smoking
- Secondary hypertension (patients with comorbidity)

3.7 Sample size calculation:

Based on an expected prevalence of Hypertension of 30% at University Teaching Hospital, Lusaka. We enrolled 46 participants, 27 in the 10PM group, 19 in the 10AM group with 3 loss to follow-up, as the patients didn't not come and unreachable by mobile. The sample size was calculated based on; two-sided significance level (1-alpha): 95, power (1-beta, % chance of detecting): 80, ratio of sample size Unexposed/Exposed: 1. Total sample size: 46, inclusive of loss to follow-up (OpenEpi, Version 2).

3.8 Data Collection Tools.

Structured data collection forms (Questionnaire) was employed to collect demographic patient specific data at enrolment and follow ups at Clinic 5. Sleep quality and duration was measured by PQSI and ESS, respectively. A PSQI score of less than 5 was considered good sleep and ESS score of less than 6 as good sleep duration. For those who cannot read, the questions were explained to them in the local language.

3.9 Data analysis.

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

3.10 Ethical Considerations.

The patients were assigned to morning and night dosing which may be away from the patient's routine. Therefore, all patients signed the written informed consent forms and the protocol was approved by the ERES Converge, Ref No.2014.Sept.008, the Research Ethics Committee for the study and clearance from University Teaching Hospital management. The patients were asked to come back in 2 weeks to avoid uncontrolled BP not attended.

Further, the information collected remained confidential. The filled questionnaires were kept in lockable cupboard and soft copy was secured with passwords.

The information was analysed immediately after the data collection was concluded to avoid unwanted access.

3.11 Study Variables.

The table below shows the variables of interest in our study and how we defined them.

Table 3.11.1 The study variables

Name	**Type**	**Definition**	**Scale**
Timing of Dosing	Independent	10AM/10PM	Categorical
Quality of Sleep	Dependent	Score:<5 good and >5, poor.	Categorical
Duration of Sleep	Dependent	Score: 1-6, good; 7-8, moderate and >9, poor.	Categorical
Sex	Independent	Male/Female	Categorical
Blood Pressure	Dependent	Mild, Moderate or Severe	Categorical
Age	Independent	Number of years	Continuous

CHAPTER FOUR

4.0 RESULTS:

The results were analysed and presented according to the objectives.

4.1 Baseline Characteristics

A total of 43 eligible individuals were included in the study and analysis. The 10AM group had 18 (41.8%), while the 10PM group had 25 (58.2%) at enrolment. Of all the participants, females were more than male as shown in Figure 4.1.1. Baseline and 12 weeks follow-up of quality and duration of sleep, and BP readings was available for 43 participants representing 97% follow up as 3 were lost to follow.

The Median and Ranges of the Ages were analyzed and presented in Table 4.1.1. While the Age distribution in the groups was represented in Figure 4.1.2.

Age in years.

Descriptive statistics for the continuous variables (table 4.1.1), showed that the meadian age of 54.5 years in AM group and median of 59 years in the PM group. The age range was 36 to 69 yeras in the AM and 35 to 75 years in the PM.

Table 4.1.1: Comparison of Median and Ranges of Age in years between the groups

	N	Median	Minimum	Maximum
AM	22	54.5	36	69
PM	21	59.0	35	75

Gender distribution in the two Groups

This study recruited more women in both groups (figure 4.1.1) with minimal differences in the AM group.

Table 4.1.2 The Gender distribution between the two groups

Timing	Sex	N	%
AM	Male	4	18.2
	Female	18	81.8
PM	Male	8	38.1
	Female	13	61.9

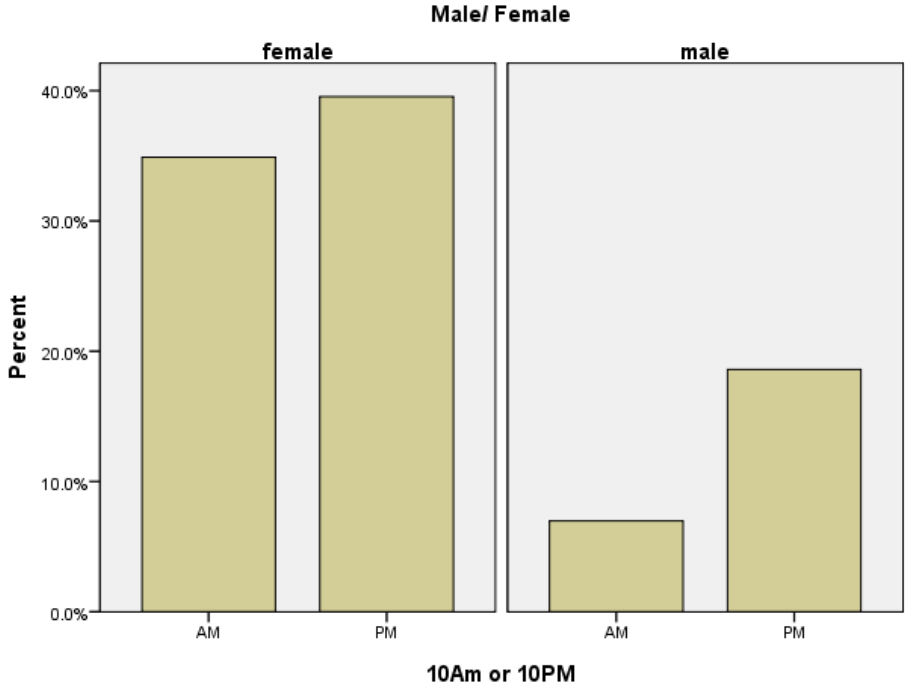

Figure 4.1.1: The gender distribution in both groups.

4.2 To determine the quality and duration of sleep differences in the morning and night timing of the dose of diuretic.

a. Quality of sleep as measured by PSQI.

The baseline sleep score by using PSQI, both groups had 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 as shown in Figures 4.2.1 to 4.2.4 (N=43).

Measure of Quality of Sleep by PSQI at all intervals of follow up

From this study findings, there was significant differences at 2, 6 and 12 weeks follow up (table 4.2.1) in the quality of sleep with p-value of less than 0.05 and end of study.

Table 4.2.1 Measure of Quality of Sleep at enrolment and follow ups.

	AM		**PM**		p
	N	%	N	%	
PSQI 0					0.092
<5	6	35.3	11	64.7	
≥5	16	61.5	10	38.7	
PSQI 2					0.021
<5	8	34.8	15	65.2	
≥5	14	70.0	6	30.0	
PSQI 8					0.002
<5	14	40.0	21	60.0	
≥5	8	100.0	0	0.0	
PSQI 12					0.010
<5	16	43.2	21	56.8	
≥5	6	100.0	0	0.0	

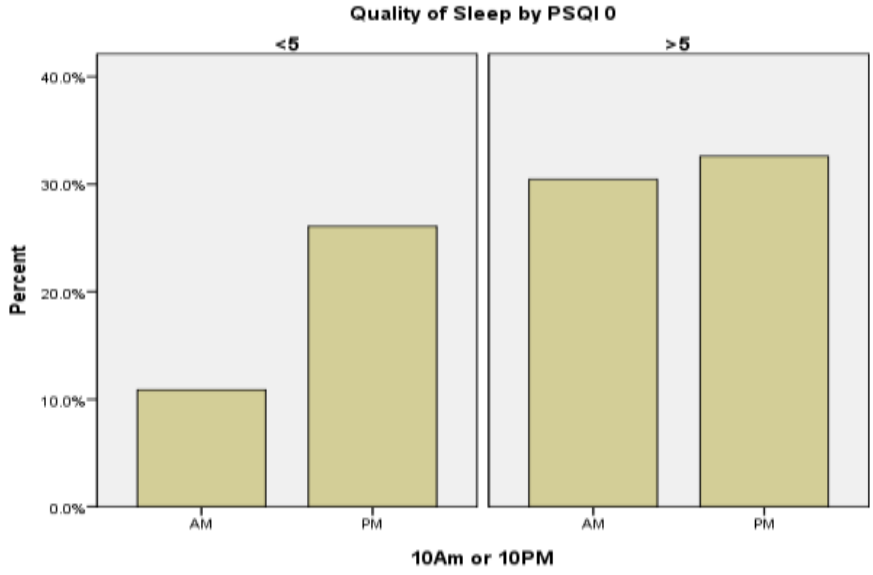

Fig 4.2.1 Comparison of quality of sleep at enrollment by PSQI

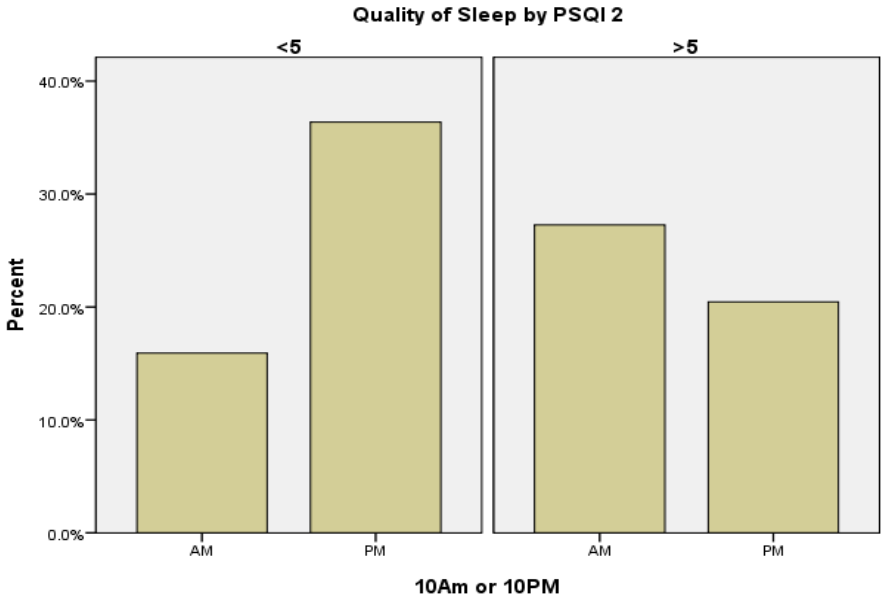

Fig 4.2.2: Comparison of quality of sleep at 2 weeks follow-up by PSQI

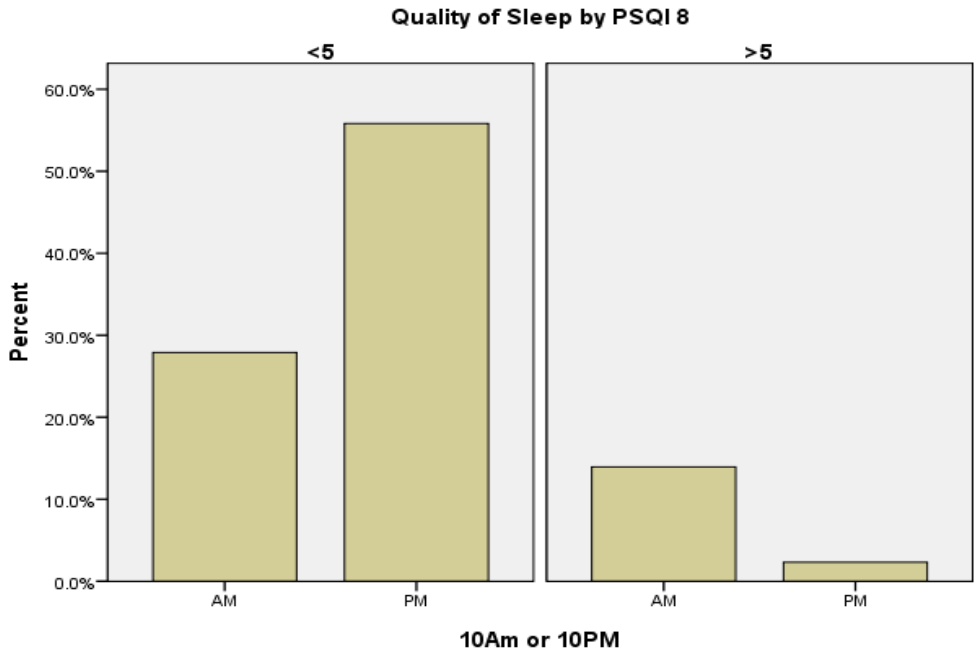

Fig 4.2.3: Comparison of quality of sleep at 8 weeks follow-up by PSQI

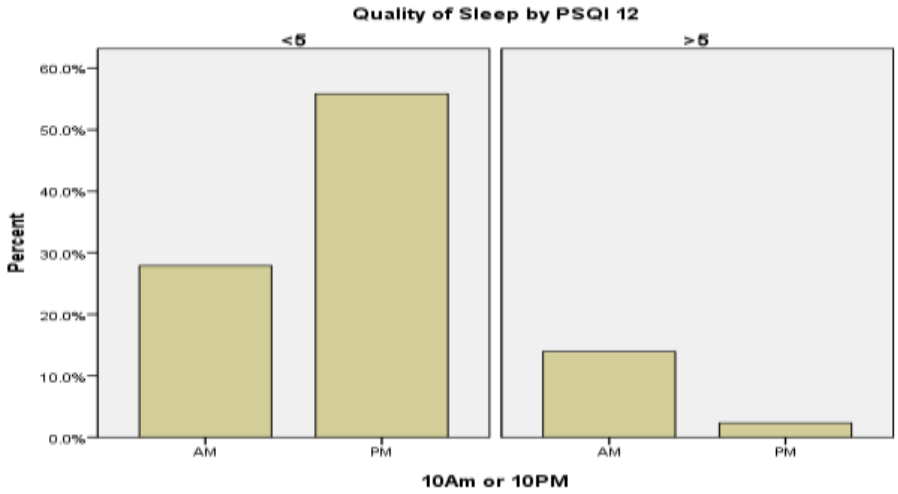

Fig 4.2.4: Comparison of quality of sleep at 12 weeks follow-up by PSQI

b. Duration of sleep as measured by ESS.

The duration of sleep was analyzed and presented in in Figures 4.2.5 to 4.2.8 for each time point of the visit (N=43). The trend shows adequate sleep in the 10 PM as the follow up continued.

Measure of Sleepliness ESS.

The findings on the sleepiness showed there was less significance differences with p-values greater than 0.05 from enrolment to 12 weeks follow up (table 4.2.2).

Table 4.2.2 The measure of Sleepiness by ESS at enrolment and follow-up

	AM		**PM**		**p**
	N	%	n	%	
ESS 0					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					0.664
0	1	100.0	0	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					0.215
0	1	100.0	0	0.0	
1-6	19	47.5	21	52.5	
7-8	2	100.0	0	0.0	
ESS 12					0.215
0	1	100.0	0	0.0	
1-6	19	47.5	21	52.5	
7-8	2	100.0	0	0.0	

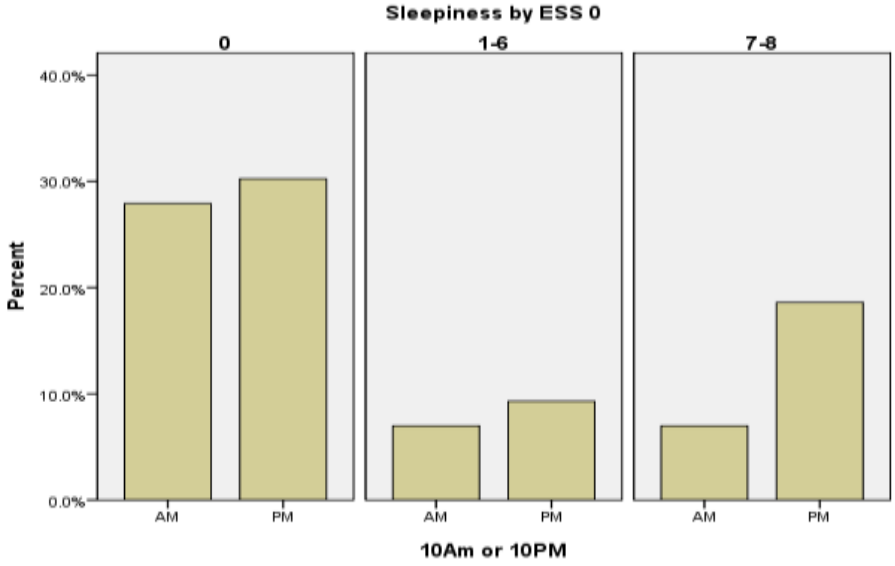

Fig. 4.2.5: Comparison of duration of sleep at enrollment.

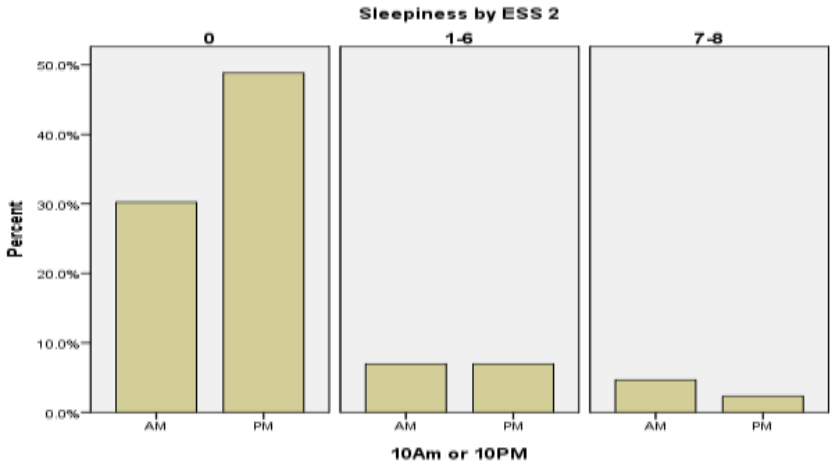

Fig.4.2.6: Comparison of duration of sleep at 2 weeks follow-up.

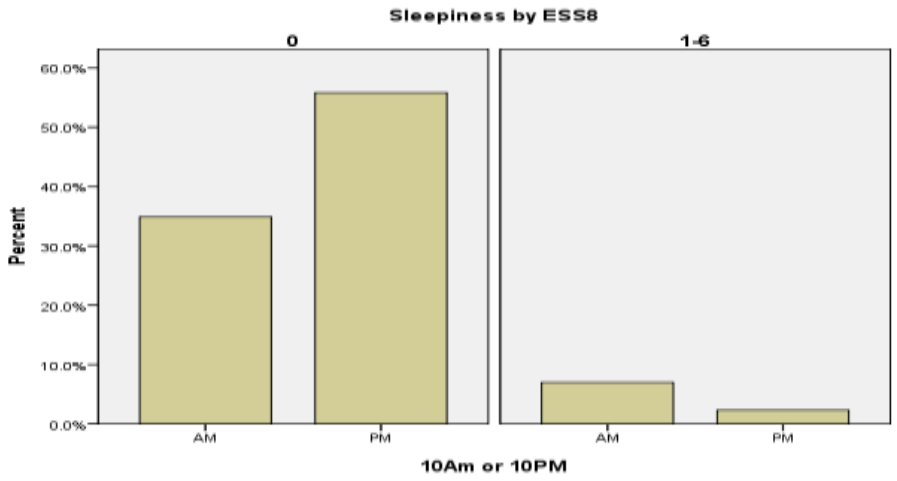

Fig.4.2.7: Comparison duration of sleep at 8 weeks follow-up.

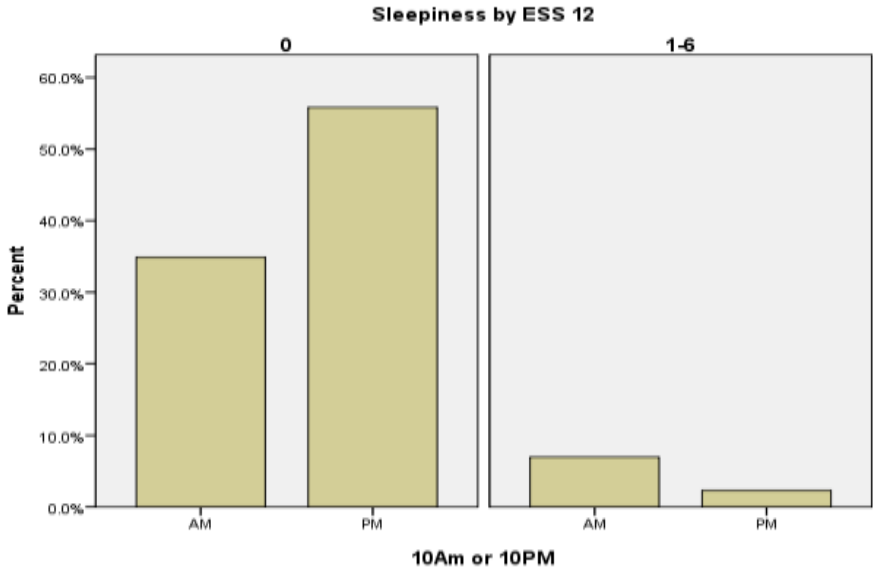

Fig. 4.2.8: Comparison of duration of sleep at 12 weeks follow-up.

4.3 The blood pressure control in the 10 AM and 10 PM dosing times.

The blood pressure readings at baseline, showing minor differences in the blood pressure control between the lowest and highest in the two groups. For all participants with BP values available for baseline up to 12 weeks follow-up, there was reduction in the 10PM dosing group as seen Figures 4.3.1 to 4.3.4 and Table 4.3.1(N=43)

Blood Pressure in the groups.

The finding of the study showed significant differences at 12 week follow up, (table 4.3.1) with the p-value of less than 0.05.

Table 4.3.1 Comparison of BP readings of enrolment and follow-ups

	AM		**PM**		**p**
	N	%	n	%	
Baseline					0.988
<140	8	50.0	8	50.0	
140-149/90-94	3	50.0	3	50.0	
150-159/95-99	11	52.4	10	47.6	
2 Weeks					0.681
140/90	11	47.8	12	52.2	
141-159/90-94	8	57.1	6	42.9	
150-159/95-99	2	40.0	3	60.0	
>160/100	1	100.0	0	0.0	
8 Weeks					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	0.0	
12 Weeks					0.020
<140/90	17	44.7	21	55.3	
141-149/90-94	5	100.0	0	0	

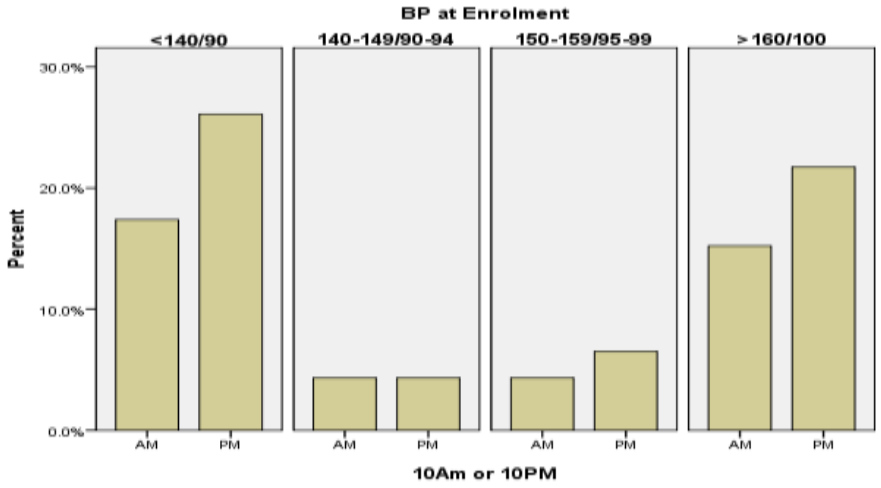

Figure 4.3.1: Comparison of BP readings at enrollment.

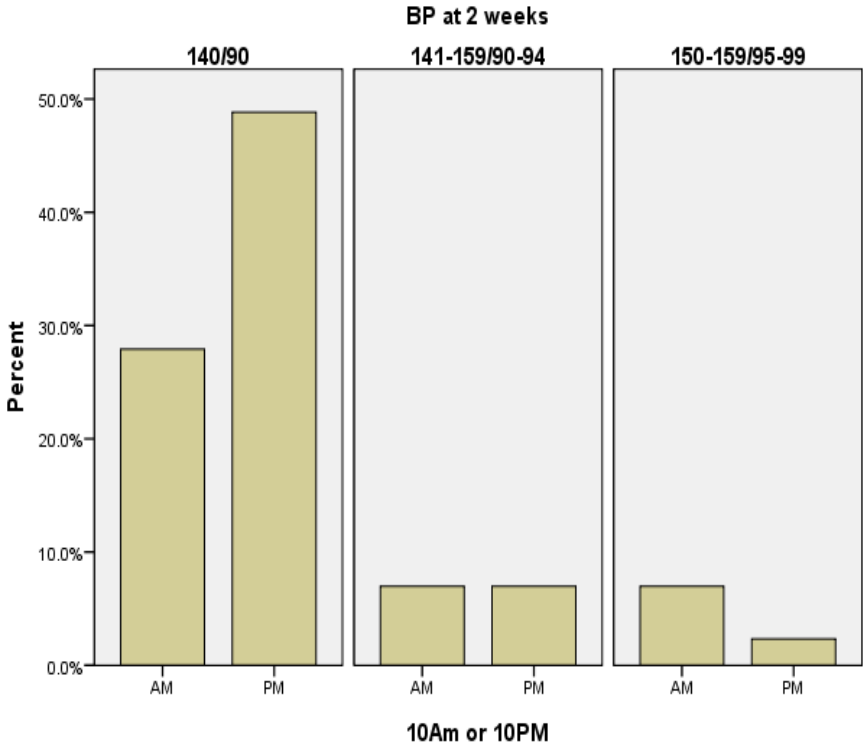

Figure 4.3.1: Comparison of BP readings at 2 weeks follow-up.

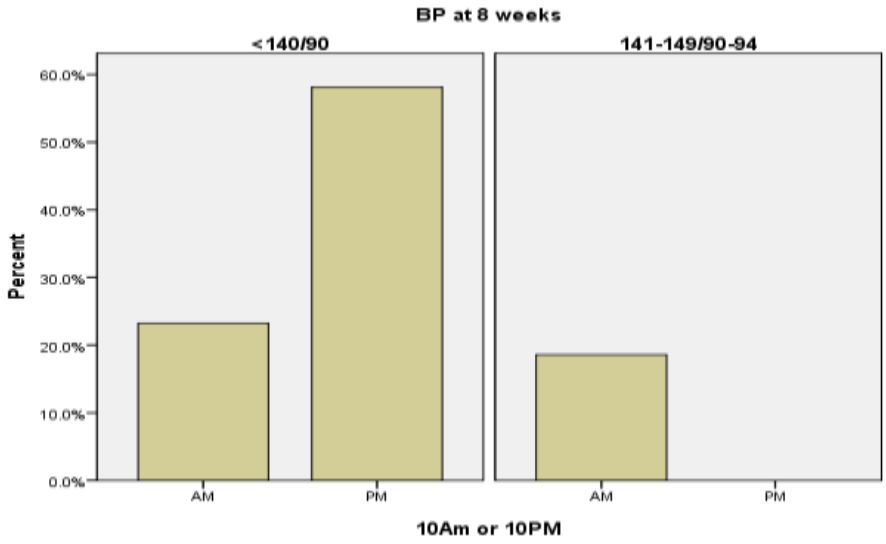

Figure 4.3.3: Comparison of BP readings at 8 weeks follow-up.

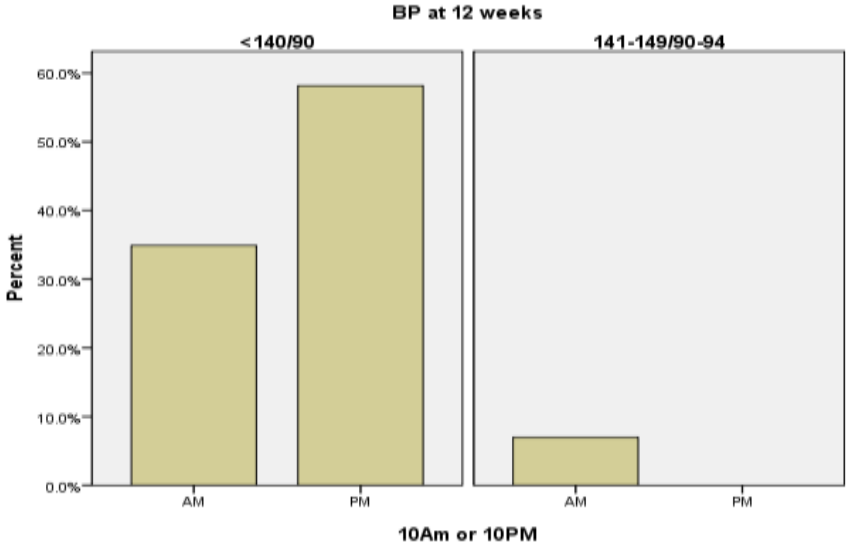

Figure 4.3.4: Comparison of BP readings at 12 weeks follow-up.

4.4 **To determine the commonly used diuretic for hypertension**.

Of participants with hypertension, overall, 16 (51.6%) in AM and 15(48.4%) in PM were on HCTZ with Amiloride drug combination (N=43).

The diuretic distribution in the two groups

The study finding on type of diuretic showed that most of our clients in both groups were on HCTZ with Amiloride combination, (table 4.4.1) though less significant.

Table 4.4.1: Type of Diuretic used in both dosing groups

	AM		**PM**		**p**
	N	%	N	%	0.924
HCTZ with Amiloride	16	51.6	15	48.4	
Furosemide	6	50.0	6	50.0	

CHAPTER FIVE

5.0 DISCUSSIONS:

On the descriptive studies, the study showed that higher percentage of women participants than men, explaining a higher prevalence of hypertension in women, 76.1% that was observed, Figure 4.1.1 and Table 4.1.2 in both groups. This was contrary to the study done by Goma and colleagues which reported that the prevalence was high in men in the study done in Lusaka (Goma *et al.*, 2011). However, in this study, it was observed that women were more willing to participate as opposed to the male counterparts.

Further, this study enrolled participants from the ages of 35-75 years with Median of 54.5 years and 59 years in AM and PM groups, respectively.

This study showed that at baseline, the majority of the participants had a score more than 5 in both groups as shown in figures 4.2.1 and 4.3.1. Despite Sleep Heart Health study not concentrating on patients on diuretics, it showed the prevalence of hypertension worsening to 60% in patients with poor sleep who were sleeping less than 5 hours in a night (Gottlieb et al., 2006). Therefore, this study agrees that when sleep is disturbed, hypertension is also poor controlled.

This study showed that sleep quality was unaffected by night time dosing of diuretics as shown in Table 4.2.1, at 2, 8 and 12 weeks follow up with p-values of 0.021, 0.002, and 0.010, respectively. However, on the sleepiness, there were no significant differences between the groups. This study therefore, agrees with Sica that diuresis due to diuretics occurs in the first 2 weeks, thereafter, vasodilatory effects takes effect (Sica, 2008). Therefore, there was no harm to administer the diuretics at 10 PM.

In contrast to Basil et al, (2012) this study looked at the quality and duration of sleep as well as BP control, and showed a positive outcome in the 10 PM dosing (study group) compared to 10 AM, with significance as follow up continued, figures 4.3.1 to 4.3.4.

At 8 and 12 weeks of follow up, this study observed that as the follow up continued; the participants provided same answers as the previous visit. This was in contrast with Wrzus et al who concluded that subjective and objective assessment of quality of sleep yield similar results (Wrzus et al., 2012).

The study showed that the blood pressure reduction was significant in the night time dosing of diuretic at the end of follow-up, figure 4.3.4. This was in line with a study done by Chikao *et al*, were 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 (hydrochlorthiazide) combination (Chikao *et al.*, 2014). This study also agrees with the study done in Nigeria, that there was pronounced BP reduction and in the 10 PM diuretic dosing compared to the 10 AM (Basil *et al.*, 2012). At 12 weeks follow up of this study, there was significant differences with p-value of 0.020, Table 4.3.1.

Despite this study using clinic BP monitoring as compared to Ambulatory Blood Pressure Monitoring (ABPM). The BP follow-up at 12 weeks showed much reduction with clinic BP monitoring, figure 4.3.4. 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 (Portaluppi and Smolensky, 2010).

Most of participants were on HCTZ with Amirolide combination type of diuretic as shown in figure 4.4.1. This could be attributed to the fact that the combination is part of the essential drug list in Zambia and first line for hypertension (Ministry of Health, 2013).

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

The 10 PM dosing of diuretic had no effect of quality and duration of sleep in hypertensive patients. There were benefits in taking diuretics in the night time as the quality of sleep seemed not to be affected amongst the hypertensive patients with night-time chronotherapy of diuretics. There was also better BP control in the night time administration as the blood pressure lowering effect was more pronounced in the 10 PM compared to the 10AM administration. It was further observed that the type of diuretic does not have significant difference, they are equally effective and quality and duration of sleep is unaffected by the type of the diuretic.

Limitations

The limitations of our study were irregular availability of HCTZ-amiloride at study site during the time which could have affected adherence to treatment in both arms. Further, the study did not assess the adherence to medications which could also affect our study. There were also limited financial resources to procure ambulatory accelerometry for objective measure of quality and duration of sleep and Ambulatory Blood Pressure Monitoring machines. There was also co- administration of other antihypertensive medicines which may have affected our outcomes.

Recommendations

1. The quality and duration of sleep was unaffected when the diuretic drugs are given in evening, therefore, they can be administered at 10 PM.
2. The BP lowering effect of diuretic was greatest in the 10 PM dosing hence the suggestion to administer them in the evening.
3. There is need for proper counselling on adequate sleep duration for better control of hypertension.
4. A regular BP check by patients is recommended for patients on medication at home.
5. Whenever the patient is on more than one BP medication, one should be administered at 10 PM inclusive of a diuretic.

6. With availability of funds, a bigger study needs to be conducted to conclusively decide the use of diuretics in the evening.

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APPENDICES

Appendix A

QUESTIONAIRE:

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Questionnaire No……..

Patient Details:

1. Initials …… Sex ……
   Age……
2. Time of medication taking……
3. Type of diuretics patient taking……

	Enrolment	At 2 weeks	At 6 weeks	At 12 weeks	Comments
BP reading					
Date					

4. Quality of Sleep assessment.

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month.

During the past Month,

1. When have you usually gone to bed?……
2. How long (in minutes) has it taken you to fall asleep each night? ……
3. What time have you gotten up in the morning? ……..
4. A) How many hours of actual sleep did you get at night?……

18 | Page

B) How many hours were you in bed?.....

5. During the past month, how often have you had trouble sleeping because	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in middle of the night or early morning				
C Have to get up to use the bathroom				
D Cannot breath comfortably				
E Cough or snore loudly				
F Feel too cold				
G Feel too hot				
H Have bad dreams				
I Have pain				
J Other reason(s), please describe, including how often you have had trouble because of this reason(s)				
6 During the past month, how often have you taken medicine to help you sleep? (POM or OTC)				
7 During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8 During the past month, how much of a problem has it been for you to keep up enthusiasm to get				

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things done?	
9 During the past month, how would you rate your sleep quality overall?	
Total	

.....

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Appendix B

The Epworth Sleepiness Scale (ESS)

How likely are you to doze off or fall asleep in following situations, in contract to feeling just tired? This refers to your usual way of life in recent times. Use the following scale to choose the most appropriate number for each situation:

0= would **never** doze

1= **slight chance** of dozing

2= **moderate chance** of dozing

3= **high chance** of dozing

SITUATION	CHANCE OF DOZING			
	0	2	6	12
Sitting and reading				
Watching Television				
Sitting inactive in a public place(e.g. a theatre or meeting)				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking to someone				
Sitting quietly after a lunch without alcohol				
In a car, while stopped for a few minutes in the traffic				
TOTAL SCORE				

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Appendix C

INFORMATION SHEET.

The Researcher

My names; **David Banda**, student at University of Zambia. I am conducting a prospective, **comparative** Cohort Study titled "Night-time chronotherapy with Diuretics: Effect on sleep quality and duration in patients with Hypertension at University Teaching Hospital in Lusaka, Zambia."

The Research

The purpose of this study is to access the quality and duration of sleep with night-time chronotherapy with diuretics, hence adding more evidence. The study will be useful to the patients for optimization of treatment with diuretics with new evidence from the study.

The Process

Participation consists of one-on-one interview, lasting approximately fifteen minutes. You will be asked a series of questions about your medication. You are encouraged to ask questions or raise concerns at any time during the interview. The interview will be repeated at 2, 8 and 12 weeks from time of enrolment. **The study will provide transport refunds for subsequent visits.**

You also have the right to withdraw from the study at any time. **You also have the right not to answer the questions which you deem sensitive**. In the event you choose to withdraw from the study all information you provide will be destroyed and omitted from the final paper.

Risk

There are minimal risks associated with participating in the study because you will continue taking the same medications, we are only going to change the time of administration; either 10AM or 10PM. At the start, there may be fluctuations in BP control, hence the reason to come back after 2 weeks after enrolment. At the end of study, we would have generated evidence and be able to optimize use of diuretics at UTH and the country in general. We will do our best to ensure that confidentiality is maintained by not citing your name and identifying information within the actual study. We

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will not share your individual responses with anyone other than the researchers. We will keep the data in a secure place and we will be the only one with access to this information. Upon completion of this project, all data will be destroyed or stored in a secure location.

If you have any questions about this study, feel free to contact the student researcher (*David Banda, davidchimbi@yahoo,co,uk, 0977966777/0955990676*). If you have any questions about your rights as a research participant, feel free to contact the Chairperson, ERES CONVERGE IRB, 33 Joseph Mwilwa, Road Rhodes Park, LUSAKA Tel: 0955 155633/4

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Appendix D

INFORMED CONSENT FORM.

Title of the Study.

Night-time chronotherapy with Diuretics: Effect on sleep quality and duration in patients with Hypertension at University Teaching Hospital in Lusaka, Zambia.

I confirm that I have read and understand the participate Information Sheet. I had an opportunity to ask questions and had them answered and I understand that all personal information will remain confidential. I understand that my participation is voluntary and that am free to withdraw at any time without giving a reason.

I agree/disagree to take part in this study.

_____ _____

Participant's signature or Thumb **Date**

_____

Interviewer's

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Appendix E

DONGOSOLO.

Wofufuza.

Maina anga ndine Davide Banda. Ndiphunzira pa University ya Zambia. Ndili kutsata maphunziro ochedwa "Phunziro la zochitika kuwodwala wa kuthamanga kwa mtima (hypertension) ngati apatsidwa mankhwala okodzetsa (Diuretics) makamaka kagonedwe ka turo pano pa chipatala chachikulu cha muno mu Lusaka, dziko la Zambia".

Kufufuza

Chilingo cha maphuzirowa ndikuona ngati wodwala agona bwino ndiponso kwa maola angati atapatsidwa mankhwala okodzetsa (Diuretics). Maphunzirowa adzatithandiza kukhala ndi fundo zopambana ndinso wodwala adzathandizika mkapatsidwe ka mankhwala.

Njira.

Kupezeka pamaphunzirowa tidzakhala pamodzi inu ndi ine. Sindidzatenga nthawi yaitali. Tidzakambitsana kwa mphindi khumi ndi zisanu. Pokambitsana mungandifunse mafunso amene akuvutani kukhosi.

Tikatha kukambitsana lero, mudzabweranso pakapita masabata awiri, ndinso mudzabwera kawiri pakapita masabata asanu ndi atatu ndipotsiriza pakapita masabata khumi ndi awiri. Ndalama zokwelera kufika kuno tizakubwezelani.

Sindikukakamizani ayi. Ndifuna muyankhe mafunso anga mwachifuniro chanu. Mwamvetsa mau anga? Ngati simufuna kuyankha mafunso ena chilikuli inu, ngati mudzafuna kuleka kugwirizana nane mukhoza kuleka nthawi ili yonse. Ndipo ndizafafaniza mafunso amene munayankha kale muphuziro yathu. Mwamvetsa bwino?

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Palibe cobvuta chiri chonse chachikulu pogwirizana nafe. Cobvutapo ndicimodzi chakuti mudzakhala muli kupatsidwa mankwala amodzimodzi kwa nthawi yosiana siana. Chinanso tidzasintha nthawi yo kupatsirani mankhwala kapena m'mawa pa ola ya khumi kufika pa ola ya mahkumi yawiri ndi awiri usiku.

Tidzagwira nchitoyi mwacheru ndikusunga chitsitsi cha zonse mudzatiuza. Sitidzapatsa kapena kuuza munthu aliyense zimene mwatifotokozera. Zonse mwatiuza tidzagwiritsa nchito ndife ndi wophunzira anzathu basi. Tidzasunga zonsezi mwacheru ndiponso pamene tatsiriza kufufuza tidzafafaniza kapena kusunga mwachitsitsi.

Ngati muli ndi funso iliyonse pama phunzirowa mukhoza kufunsa a Davide Banda pomuyimbila lamya pa 0977966777 kapena 0955990676. Ngati pali mafunso okudza pa ufulu wanu pa maphuzirowa funsani Musogoleli wa ERES CONVERGE IRB, 33 Josepha Mwlwa Road, Rhodes Park LUSAKA kapena lamya 0955155633/4.

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CHIMVOMEREDZI

Mutu wa phunziro.

Phunziro la zochitika kuwodwala wa kuthamanga kwa mtima (hypertension) ngati apatsidwa mankhwala okodzetsa (Diuretics) makamaka kagonedwe ka turo.

Ndawerenga ndi kumvetsetsa dongosolo la maphunzirowa. Pazomwe sindinamvetsetse kapena ku tsatira ndinafunsa ndipo mafunso yanga yanayankhidwa mo kwanira.

Anandifotokonzeraso kuti nkhani zonse zokudza ine zidzakhala zacisinsi.

Ndikuchita zonsezi mwachifuniro changa osakakamizidwa ndipo ngati nafuna ndingasiye kugwirizana nawo amaphunzirowa.

Ndibvomera/ sindibvomera kugwirizana nanu pamaphunziro amenewa.

Dzina .....

Kusaina. **Tsiku**

Dzina la ofufunza

APPROVED
19 JAN 2015
ERES CONVERGE
P/BAG 125, LUSAKA.

Appendix F

ERES CONVERGE

Cell: +260 966 765 503
Email: eresconverge@yahoo.co.uk

I.R.B. No. 00005948
F.W.A. No. 00011697

19th January, 2015

Ref. No. 2014-Sept-008

The Principal Investigator
Mr. David Banda
University Teaching Hospital
Dept. of Pharmacy
P/Bag RW 1X,
LUSAKA

Dear Mr. Banda,

RE: NIGHT TIME CHRONO THERAPY WITH DIURETICS: EFFECT ON SLEEP QUALITY AND DURATION IN PATIENTS WITH HYPERTENSION AT UNIVERSITY TEACHING HOSPITAL.

Reference is made to your corrections dated 28th November, 2014. The IRB resolved to approve this study and your participation as principal investigator for a period of one year.

Review Type	Ordinary	Approval No. **2014-Sept-008**
Approval and Expiry Date	Approval Date: 19th January, 2015	Expiry Date: 18th January, 2016
Protocol Version and Date	Version-Nil	18th January, 2016
Information Sheet, Consent Forms and Dates	• English, Nyanja.	18th January, 2016
Consent form ID and Date	Version-Nil	18th January, 2016
Recruitment Materials	Nil	18th January, 2016
Other Study Documents	Questionnaire, Epworth Sleepiness Scale.	18th January, 2016
Number of participants approved for study	74	18th January, 2016

Specific conditions will apply to this approval. As Principal Investigator it is your responsibility to ensure that the contents of this letter are adhered to. If these are not adhered to, the approval may be suspended. Should the study be suspended, study sponsors and other regulatory authorities will be informed.

Conditions of Approval

- No participant may be involved in any study procedure prior to the study approval or after the expiration date.
- All unanticipated or Serious Adverse Events (SAEs) must be reported to the IRB within 5 days.
- All protocol modifications must be IRB approved prior to implementation unless they are intended to reduce risk (but must still be reported for approval). Modifications will include any change of investigator/s or site address.
- All protocol deviations must be reported to the IRB within 5 working days.
- All recruitment materials must be approved by the IRB prior to being used.
- Principal investigators are responsible for initiating Continuing Review proceedings. Documents must be received by the IRB at least 30 days before the expiry date. This is for the purpose of facilitating the review process. Any documents received less than 30 days before expiry will be labelled "late submissions" and will incur a penalty.
- Every 6 (six) months a progress report form supplied by ERES IRB must be filled in and submitted to us.
- ERES Converge IRB does not "stamp" approval letters, consent forms or study documents unless requested for in writing. This is because the approval letter clearly indicates the documents approved by the IRB as well as other elements and conditions of approval.

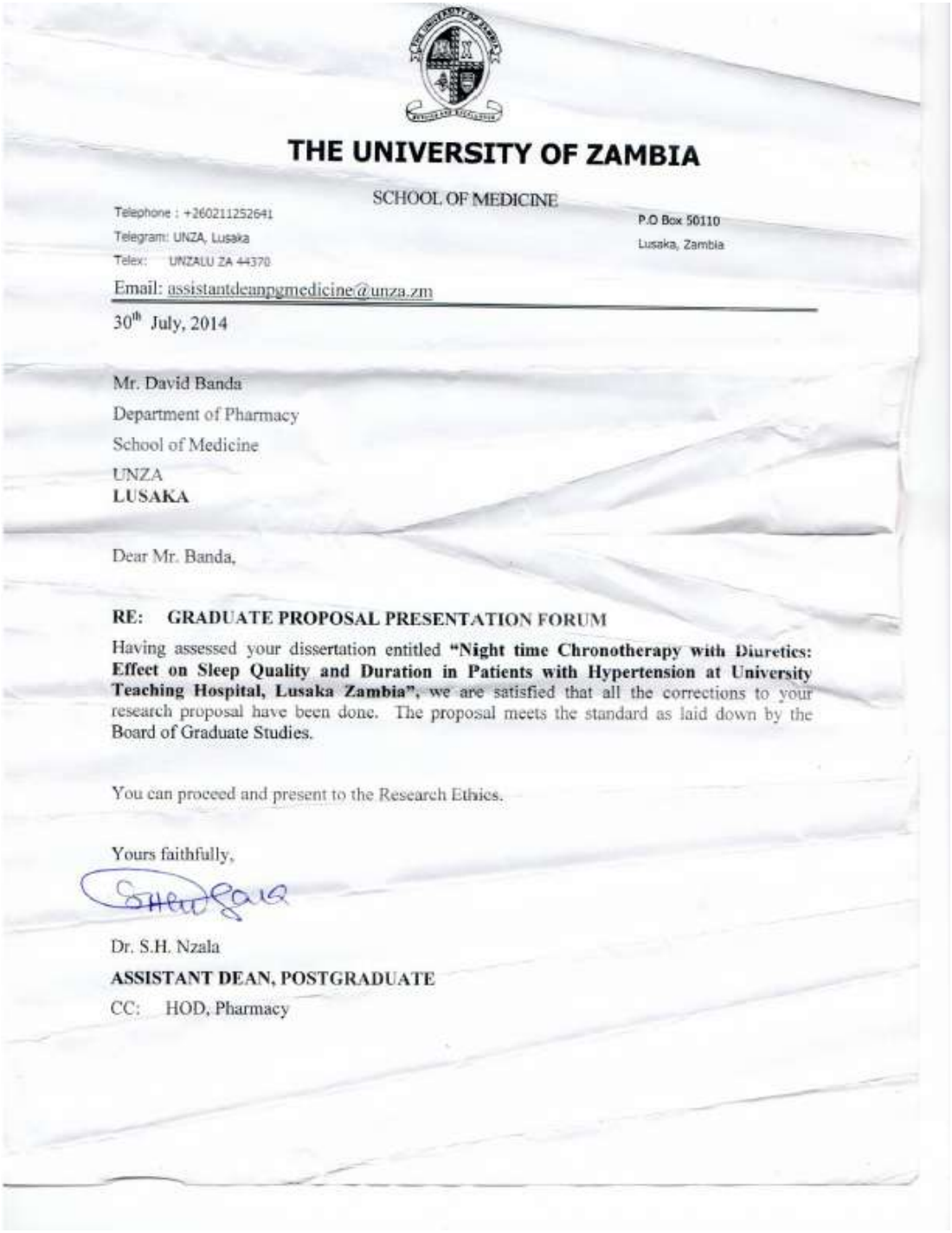
Should you have any questions regarding anything indicated in this letter, please do not hesitate to get in touch with us at the above indicated address.

On behalf of ERES Converge IRB, we would like to wish you all the success as you carry out your study.

Yours faithfully,
ERES CONVERGE IRB

Dr. E. Munalula-Nkandu
BSc (Hons), MSc, MA Bioethics, PgD R/Ethics, PhD
CHAIRPERSON

Appendix G



THE UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

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Telegram: UNZA, Lusaka
Telex: UNZALU ZA 44370
P.O Box 50110
Lusaka, Zambia
Email: assistantdeanpgmedicine@unza.zm

30th July, 2014

Mr. David Banda
Department of Pharmacy
School of Medicine
UNZA
LUSAKA

Dear Mr. Banda,

RE: GRADUATE PROPOSAL PRESENTATION FORUM

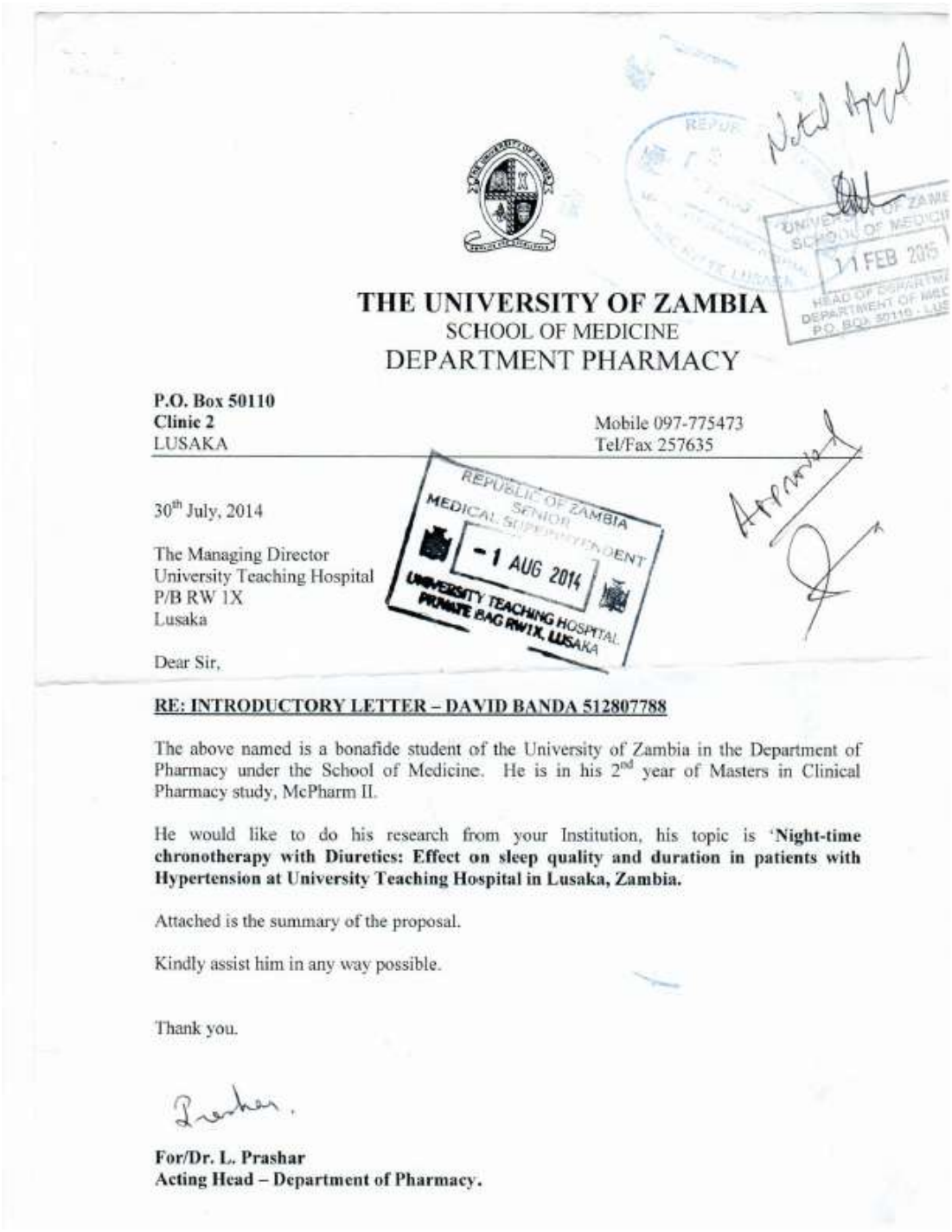
Having assessed your dissertation entitled **"Night time Chronotherapy with Diuretics: Effect on Sleep Quality and Duration in Patients with Hypertension at University Teaching Hospital, Lusaka Zambia"**, we are satisfied that all the corrections to your research proposal have been done. The proposal meets the standard as laid down by the Board of Graduate Studies.

You can proceed and present to the Research Ethics.

Yours faithfully,

Dr. S.H. Nzala
ASSISTANT DEAN, POSTGRADUATE
CC: HOD, Pharmacy

Appendix H



THE UNIVERSITY OF ZAMBIA
SCHOOL OF MEDICINE
DEPARTMENT PHARMACY

P.O. Box 50110
Clinic 2
LUSAKA

Mobile 097-775473
Tel/Fax 257635

30th July, 2014

The Managing Director
University Teaching Hospital
P/B RW 1X
Lusaka

Dear Sir,

RE: INTRODUCTORY LETTER – DAVID BANDA 512807788

The above named is a bonafide student of the University of Zambia in the Department of Pharmacy under the School of Medicine. He is in his 2nd year of Masters in Clinical Pharmacy study, McPharm II.

He would like to do his research from your Institution, his topic is '**Night-time chronotherapy with Diuretics: Effect on sleep quality and duration in patients with Hypertension at University Teaching Hospital in Lusaka, Zambia.**

Attached is the summary of the proposal.

Kindly assist him in any way possible.

Thank you.

For/Dr. L. Prashar
Acting Head – Department of Pharmacy.