ABSTRACT

Hypertension has been a major public health issue and is common among all the ages indeed. In coming years frequency is expected to be increase considerably. According to International Society of Hypertension (ISH) patients with hypertension will progress to cross 1.56 billion by 2025! chronobiology has important effects on a drug's action. Blood pressure (BP) follows a circadian rhythm, with BP levels falling during sleep and increasing in the early morning hours in most individuals. The current prospective study is based on the chronological effects of morning Vs bed time administration of the most commonly prescribed antihypertensives in a tertiary care hospital and which is beneficial. Chronotherapeutics is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects. A sample size of 178 patients has been chosen from the study site limiting to the inclusion criteria precisely. Majorly the drugs chosen for this study were ARBs, calcium channel blockers and beta blockers which are most commonly used in any tertiary care hospital. Among the three classes of drugs calcium channel blockers showed a significant difference from the baseline when administered in the morning than evening, the remaining classes which were taken into consideration did not show any significant differences from baseline blood pressure. This experimental study gives us the potential drug administration and knowing the effective therapeutic potency of the drugs. On the other hand, physicians and practitioners all over the world should guide the public regarding the high or low blood pressure may be the major signs that many other body organs are in high risk. The message conveyed should be in such a way it should make every individual think regarding the unhealthy lifestyle consequences.
KEYWORDS: Chronobiology, circadian rhythm, drug administration, chronotherapeutics, chronological effects.

BACKGROUND
Hypertension has been a major health public issue and is common among all the ages indeed. In coming years frequency is expected to be increase considerably. According to International Society of Hypertension (ISH) 972 million adults were affected with blood pressure issues i.e. either high or low in year 2000, which will progress to cross 1.56 billion by 2025! Generalized lifestyle factors, such as physical inactivity, diet rich in salt, highly processed foods, alcohol and tobacco use, leads to proliferation of disease burden and in developed countries like INDIA, CHINA and African countries it is spreading vigorously at alarming rate. On the other hand, physicians and practitioners all over the world should guide the public regarding the high or low blood pressure may be the major signs that many other body organs are in high risk. The message conveyed should be in such a way it should make every individual think regarding the unhealthy lifestyle consequences.

INTRODUCTION
According to WHO hypertension is a common disease that is simply defined as persistently elevated arterial Blood Pressure (BP). It is also defined as sustained systolic pressure greater than 140 mmHg accomplished by an elevated diastolic pressure is greater than 90 mmHg. BP is classified on the basis of systolic and diastolic values.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic Pressure mmHg</th>
<th>Diastolic Pressure mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre hypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Hypertension Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension Stage 2</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

ETIOLOGY
In most patients, hypertension results from an unknown pathophysiologic aetiology (essential or primary hypertension). This form of hypertension cannot be cured, but it can be controlled.

A small percentage of patients have a specific cause of their hypertension (secondary hypertension). There are many potential secondary causes that are either concurrent to
medical conditions or are endogenously induced. If the cause can be identified, hypertension in these patients has the potential to be cured.

**Essential Hypertension**

More than 90% of individuals with hypertension have essential hypertension. Numerous mechanisms have been identified that may contribute to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible.

- Genetic factors may play an important role in the development of essential hypertension.
- Many of the genetic traits feature genes that affect sodium balance, nitric oxide release, and excretion of aldosterone, other adrenal steroids, and angiotensinogen are also documented.

**Secondary Hypertension**

Fewer than 10% of patients have secondary hypertension where either a co morbid disease or drug is responsible for elevating BP. In most of these cases, renal dysfunction results from severe chronic kidney disease or renovascular disease is the most common secondary cause. Certain drugs, either directly or indirectly, can cause hypertension or exacerbate hypertension.

**EPIDEMIOLOGY**

Approximately 31% of the population (72 million Americans) has high BP (140/90 mm Hg). The percentage of men with high BP is higher than that of women before the age of 45 years, but between the ages of 45 and 54 years the percentage is slightly higher with women. After age 55 years, a much higher percentage of women have high BP than men.

BP values increase with age, and hypertension (persistently elevated BP values) is very common in the elderly. The lifetime risk of developing hypertension among those 55 years of age and older who are normotensive is 90%.

**PATHOPHYSIOLOGY**

**underlying hemodynamic effect**

BP can be expressed as the product of cardiac output and peripheral resistance:

\[ BP = CO \times PR \]
So an elevated BP implies that one or both of these factors must also be expressively raised. Raised cardiac output is the prime cause. Fluid retention which is known to be an occasional cause of hypertension (secondary).

In hemodynamic terms blood volume is increased, venous return and preload are raised and cardiac output rises initially. The systemic peripheral resistance would increase, as part of the normal auto regulation of blood flow to limit the resulting excessive perfusion. Cardiac output would then return to normal. Thus possible causes for an initially high cardiac output or circulating blood volume are currently being investigated; there is a link here with the SALT HYPOTHESIS.

**Primary and Secondary Hypertension**

In about 10 percent of cases there may be very obvious reasons for an elevated pulse rate or cardiac output. In majority of the cases there is usually only a mild or moderate elevation of BP for which no obvious causes can be ruled out. The body resists attempts to lower the pressure. It seems the body’s pressure control mechanism has been reset higher. Hence it is termed “ESSENTIAL HYPERTENSION”.

**Accelerated Hypertension**

Accelerated hypertension is a disease characterized by a rapid and sudden increase in blood pressure over the baseline level that, if untreated, poses a threat for damage to organs and tissues.

**Hypertensive Crisis**

A hypertensive crisis is a severe increase in blood pressure that can lead to a stroke. Extremely high blood pressure — a systolic blood pressure of 180 millimeters of mercury (mm Hg) or higher & diastolic blood pressure of 120 mm Hg or higher — damages blood vessels. They become inflamed and may leak fluid or blood.

Hypertensive crises can present as hypertensive *urgency* or as a hypertensive *emergency*.

**Hypertensive Urgency**

Hypertensive *urgency* is a situation where the blood pressure is severely elevated [180 or higher for your systolic pressure (top number) or 110 or higher for your diastolic pressure (bottom number)], but there is no associated organ damage. Those experiencing hypertensive urgency may or may not experience one or more of these symptoms.
• Severe headache
• Shortness of breath
• Nosebleeds
• Severe anxiety

**Hypertensive Emergency**
A hypertensive emergency exists when blood pressure reaches levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 systolic OR 120 diastolic, but can occur at even lower levels in patients whose blood pressure had not been previously high.

**SOME CAUSES OF SECONDARY HYPERTENSION**
• Glomerular damage
• Increased rennin secretion
• Vasomotor constriction
• Aortic coarctation
• Iatrogenic

**PATHOGENESIS OF ESSENTIAL HYPERTENSION**
Most theories of hypertension implicate the kidney. This creates a difficulty because renal damage is commonly a consequence of prolonged hypertension owing to damage to renal arterioles. Renal damage raises blood pressure which in turn causes further renal damage. Renal damage found in a patient with hypertension of intermediate duration could be either a cause or consequence.

**CLINICAL PRESENTATION OF HYPERTENSION**
Generally the patient may appear very healthy, or may have the presence of additional cardiovascular (CV) risk factors.
• Age (≥55 years for men and 65 years for women)
• Diabetes mellitus
• Dyslipidemia (elevated low-density lipoprotein-cholesterol, total cholesterol, and/or triglycerides; low high-density lipoprotein-cholesterol)
• Microalbuminuria
• Family history of premature CV disease
• Obesity (body mass index ≥30 kg/m²)
• Physical inactivity
• Tobacco use

SIGN & SYMPTOMS
Mild to moderate essential hypertension is usually asymptomatic.

Accelerated hypertension: Accelerated hypertension is associated with headache, drowsiness, confusion, vision disorders, nausea, and vomiting.

Secondary hypertension: Some additional signs and symptoms suggest that the hypertension is caused by disorders in hormone regulation.

Hypertension combined with obesity distributed on the trunk of the body, accumulated fat on the back of the neck ('buffalo hump'), wide purple marks on the abdomen (abdominal striae), or the recent onset of diabetes suggests that an individual has a hormone disorder known as Cushing's syndrome.

In pregnancy: increased blood pressure in pregnant women may lead to a condition that typically starts from 20th week of pregnancy known as preeclampsia. Pre-eclampsia causing seizure leading to Elcampsia condition which may be a fatal death. Though its anot proven how to prevent pre-eclampsia.

In children: Some signs and symptoms are especially important in newborns and infants such as failure to thrive, seizures, irritability, lack of energy, and difficulty breathing.

PHARMACOTHERAPY
TREATMENT GOALS
• To reduce CV and renal morbidity and mortality
• Identification and treatment of all risk factors
• Management of associated clinical conditions
• Treatment of elevated BP
• Targeted BP for patients with pre hypertension

Categories of drugs used
• ACE inhibitors
- Alpha blockers
- Angiotensin II Antagonists
- Beta blockers
- Calcium antagonists
- DihydropyridineCa Antagonists
- Benzothiazepine&PhenylalkylamineCa Antagonists
- Diuretics
- Centrally acting agents
- Direct vasodilators.

**Ace Inhibitors**

**ACTION**-Blocks the conversion of Angiotensin I to Angiotensin II by inhibiting ACE.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose</th>
<th>Maintenance dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>10mg, PO, OD</td>
<td>May increase to 20mg per day</td>
<td>Cough, fatigue and dizziness</td>
</tr>
<tr>
<td>Captopril</td>
<td>12.5-25mg, PO, BID/TID May increase gradually to 50 mg, PO, BID/TID</td>
<td>unexplained rash, cough, and decrease or loss of taste</td>
<td></td>
</tr>
<tr>
<td>Cilazapril</td>
<td>1.25mg, PO, OD for 2 days Maintenance dose 2.5mg-5mg, PO, OD</td>
<td>light-headedness, dry cough</td>
<td></td>
</tr>
<tr>
<td>Delapril</td>
<td>15mg, PO, OD Maximum dose-120mg/day</td>
<td>Dizziness, head ache, fatigue</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>(on diuretic) 2.5mg, OD (no diuretic) 5mg, OD</td>
<td>Hypotension, dry cough</td>
<td></td>
</tr>
</tbody>
</table>

ACE inhibitors are well tolerated with low frequency of side effects. Maybe used as monotherapy or in combination with beta blockers, calcium antagonists, or diuretics. Side effects are uncommon and include rash, angioedema, proteinuria, or leukopenia, particularly in pts with elevated serum creatinine. A nonproductive cough may develop in the course of therapy in up to 10% of patients, requiring an alternative regimen. Note that renal function may deteriorate as a result of ACE inhibitors in patients with bilateral renal artery stenosis.

**Alpha Blockers**

**ACTION**- Lowers BP by reducing peripheral resistance and also reduces prostatic and Urethral smooth muscle tone

- Provides symptomatic relief for patients with early BPH.
- Favourable effect on lipid metabolism.
Bunazosin  | Initial dose- 1.5 mg/day  
May increase to 3-6mg/day | Tachycardia, Orthostatic hypotension  

Prazosin  | Initial dose- 0.5mg BID/TID  
increased gradually every 4-7 days  
Maximum dose- 20mg/day | orthostatic hypotension, syncope, and nasal congestion  

Terazosin  | Initial dose- 1mg, OD at bedtime  
Maximum dose- 20mg/day | Dizziness, drowsiness, lightheadedness.  

Doxazosin  | Initial dose- 1mg, OD  
Maximum dose 16mg/day | Nasal congestion, tiredness, weakness.  

**Angiotensin II Antagonist**  
**ACTION- Blocks type II angiotensin receptor**  

<table>
<thead>
<tr>
<th>Angiotensin II Antagonist</th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>4mg, OD</td>
<td>16mg/day</td>
<td>Back pain, diarrhea, dizziness</td>
</tr>
<tr>
<td>Eposartan</td>
<td>600mg, OD in morning</td>
<td>800mg/day</td>
<td>Back pain, dizziness.</td>
</tr>
<tr>
<td>Losartan</td>
<td>50mg, OD</td>
<td>50-100mg</td>
<td>Diarrhea, dizziness, tiredness.</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>20-40mg, OD</td>
<td>80mg/day</td>
<td>Sore throat, upper respiratory tract infection.</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80mg, OD</td>
<td>May increase to 160mg, OD</td>
<td>Dizziness, headache.</td>
</tr>
</tbody>
</table>

These are suitable for initiation and maintenance therapy.  
Beneficial effect in early and advanced type 2 diabetes mellitus neuropathy.  
**EFFECT-** Causes vasodilation and a fall in BP.  

**Beta Blockers**  
**ACTION:** Competitive antagonist of the effects of catecholamine at beta adnergic sites, beta 2 receptor blockade can increase bronchial resistance and inhibition of catecholamine induce glucose metabolism.  

<table>
<thead>
<tr>
<th>Beta Blockers</th>
<th>Initial dose</th>
<th>Maximum dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>200mg, PO, BID</td>
<td>800mg/day</td>
<td>Constipation, diarrhea, dizziness</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>75mg-100mg/day, PO, TID</td>
<td>Bradycardia, hypotension</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-100mg, PO, OD</td>
<td>200mg/day</td>
<td>Tiredness and dizziness</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50-100m,PO, OD</td>
<td>400mg/day</td>
<td>Tiredness, slow heart rate</td>
</tr>
<tr>
<td>Propranolol</td>
<td>10- 80mg, PO, BID</td>
<td>640mg/ day</td>
<td>Fever, sore throat, and headache.</td>
</tr>
<tr>
<td>Bisprolol</td>
<td>5mg, PO, OD</td>
<td>40mg/day</td>
<td>Abdominal cramps, diarrhea</td>
</tr>
</tbody>
</table>
Particularly effective in young pts with “hyperkinetic” circulation. Begin with low dosage (e.g., Atenolol 25 mg QD).

Relative contraindications: Bronchospasm, CHF, AV block, bradycardia, and “brittle” insulin-dependent diabetes.

**Diuretics**

**ACTION** - Reduce the risk of fatal & non fatal stroke and have been shown to reduce CV morbidity and mortality at all causes.

Thiazides preferred over loop diuretics because of longer duration of action; however, the latter are more potent when Glomerular filtration rate ≤ 25 mL/min. Major side effects include hypokalemia, hyperglycemia and hyperuricemia, which can be minimized by using low dosage.

**Aldosterone Antagonists**

Spironolactone - 50-100mg/day, Maximum dose 200mg/day
ADR- ataxia, erectile dysfunction, drowsiness

**Loop Diuretics**

Bumetadine - 0.5-2mg/day, PO, Max dose 5-10mg/day.
ADR- Dizziness or lightheadedness.
Furosemide - 20-80mg, PO, OD
ADR- Dizziness or lightheadedness.

**Potassium Sparing Diuretics**

Amiloride - 5-10mg, PO, OD, Max dose 20mg/day.
ADR- Diarrhea, headache, loss of appetite

**Thiazide Diuretics**

1) Chlorothiazide - 250-500mg/day, PO, OD
ADR- Blurred vision, dizziness, headache
2) Chlorthalidone - 25-100mg, PO, OD
ADR- Constipation, dizziness, headache
3) Cyclospentiazide - 0.25-1.5mg, PO, OD
ADR- Electrolyte imbalance, hyperglycaemia, gout
4) Hydrochlorothiazide - 12.5mg, PO, OD  
ADR- Constipation, diarrhea, dizziness

NONPHARMACOLOGIC THERAPY

- Hypertension is two to three times more likely in overweight than in lean persons. More than 60% of patients with hypertension are overweight.
- Diets rich in fruits and vegetables and low in saturated fat lower BP in patients with hypertension.
- Most people experience some degree of SBP reduction with sodium restriction.
- Cigarette smoking is a major, independent, modifiable risk factor for CV disease. So quit smoke as soon as possible.

CHRONOBIOLOGY AND HYPERTENSION

Chronobiology has important effects on a drug’s action. Blood pressure (BP) follows a circadian rhythm, with BP levels falling during sleep and increasing in the early morning hours in most individuals. Most patients, however, receive all of their drugs in a single morning dose.

Chronotherapeutics has been defined as the purposeful timing of medications to proportion their serum and tissue concentrations in synchrony with known circadian rhythms in disease processes and symptoms as a means of enhancing beneficial outcomes and/or attenuating or averting adverse effects. Chronotherapeutics is the purposeful alteration of drug level to match rhythms to optimize therapeutic outcomes and minimize size effects.

For the treatment of hypertension, this idea has the potential for a therapeutic paradigm shift. Chronotherapy involves the administration of medication in coordination with the body's circadian rhythms to maximise therapeutic effectiveness and minimise/avoid adverse effects. Chronotherapy provides a means of individualizing treatment of hypertension according to the circadian profile of blood pressure of each patient.

The chronotherapeutic strategy constitutes a new option to optimize blood-pressure control and to reduce risk.

Antihypertensive medications may display a circadian time-dependency in their pharmacokinetics and effects. BP exhibits considerable variation during the day and follows a
circadian rhythm, with SBP and DBP falling during sleep and rising rapidly with the start of morning activity.

In patients with essential hypertension, the day-night pattern of blood pressure change is generally similar to that of normotensives, with a significant nocturnal blood pressure fall. Blood pressure variability and the blunted nocturnal fall in blood pressure may be clinically relevant. Several studies have demonstrated that subjects whose 24-h variability was higher than the group average were more likely to have target-organ damage.

If a once-daily antihypertensive agent is given in the morning, it is important that it maintains BP control throughout the day-time and night-time periods, particularly towards the end of the dosing interval, to cover the critical early morning hours.

To better ensure coverage during the night-time and early morning periods, dosing of antihypertensive agents, particularly ARBs, at bedtime has been recommended, with a number of studies providing support. Antihypertensive treatment that reduces blood pressure variability and preserves the nocturnal fall in blood pressure will help to protect target organs in hypertension.

Several studies with angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme (ACE)-inhibitors, both agents that reduce the renin–angiotensin–aldosterone system (RAAS) activity, have reported improvements in night-time BP and a reduction in the early morning rise in BP with bedtime dosing compared with traditional dosing upon awakening.

The proposed mechanism for the benefit of night-time dosing of the ACE-inhibitor or ARB is ascribed to more effective RAAS blockade during the sleep and early morning periods.

The pharmacologic rationale for more effective BP lowering with evening dosing of antihypertensive therapy presupposes the inability of morning dosing to effectively lower BP at night and during the early morning period. This cannot be supported, however, as studies that evaluated morning versus evening administration of amlodipine, a long-acting calcium channel blocker (circulating half-life >24h), reported no benefit of evening versus morning dosing.
Several of these known abnormalities can be modified by clinical interventions, including proper timing of antihypertensive drug therapy and use of classes of antihypertensives for which a substrate exists to induce a pharmacologic effect.

It is particularly important to use therapies that will provide control throughout a 24-hour dosing interval. Morning administered amlodipine had a better effect on the circadian BP compared with evening administrated amlodipine in mild-to-moderate essential hypertension.

Differences in efficacy depending on the time of day of drug administration lead to differences in effects on the circadian pattern of BP and, in particular, on the nocturnal decline relative to the diurnal mean of BP.

Chronotherapy provides a means of individualizing treatment of hypertension according to the circadian BP profile of each patient, and constitutes a new option to optimize BP control and reduce risk.

**REVIEW OF LITERATURE**

<table>
<thead>
<tr>
<th>S.no</th>
<th>Author</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>Hermida et al.</td>
<td>ARB’s had a mildly better effect in lowering blood pressure when administered in the evening when compared to morning administration.</td>
</tr>
<tr>
<td>II.</td>
<td>Zappe et al.</td>
<td>Highly significant changes were not seen in morning vs bedtime dosing of ARB’s.</td>
</tr>
<tr>
<td>III.</td>
<td>Hermida et al.</td>
<td>Telmesartan administered at bedtime, as opposed to morning dosing, improved the sleep time-relative blood pressure decline without a loss in 24-hour efficacy.</td>
</tr>
<tr>
<td>IV.</td>
<td>Qiu et al.</td>
<td>In contrast to their study nocturnal BP regulation was significantly achieved with bedtime dosing of amlodipine.</td>
</tr>
<tr>
<td>V.</td>
<td>Kaur G. et al.</td>
<td>Better 24-hour blood pressure was maintained when Beta blockers were administered as morning doses</td>
</tr>
<tr>
<td>VI.</td>
<td>Nold G. et al.</td>
<td>Bedtime administered amlodipine decreases the early morning rise in blood pressure which may be advantageous in reducing the early morning cardiovascular risk.</td>
</tr>
<tr>
<td>VII.</td>
<td>Barry et al.</td>
<td>Beta blockers have time-dependent pharmacokinetics and perform better with morning doses.</td>
</tr>
<tr>
<td>VIII.</td>
<td>Barry et al.</td>
<td>Beta blockers have time-dependent pharmacokinetics and perform better with</td>
</tr>
</tbody>
</table>
morning doses.

IX. White W B et al. 24-hour normal blood pressure can be maintained only on administering beta blockers as morning doses.

X. Neutel JM et al. Angiotensin II receptor blockers for 24-hour blood pressure control are more effective as morning doses though not less effective as bedtime doses either.

XI. Ayala DE et al. Circadian pattern of ambulatory blood pressure in hypertensive patients with type 2 diabetes is better maintained in patients taking morning doses of telmesartan.

XII. Xavier D et al. Pattern of drug use in hypertension in a tertiary hospital shows more use of telmesartan than valsartan and other classes of antihypertensives.

XIII. Hansson L et al. Lowering hypertension can be better achieved by once daily doses of amlodipine at bed time than as morning doses.

XIV. Ohta Y et al. Improvement of blood pressure control in a hypertension clinic was seen when telmesartan was prescribed as once daily morning doses and amlodipine was prescribed as once daily nighttime doses.

XV. Gosse P et al. Morning doses of CCB’s were not as effective as bedtime doses.

AIM AND OBJECTIVE OF WORK

Aim
The aim of this study is to compare the antihypertensive effects dosing of the most commonly prescribed monotherapeutic anti-hypertensives in a tertiary care hospital.

Objective
To evaluate whether time of administration has an effect on regulation of blood pressure in patients receiving monotherapy with antihypertensives with a focus on Telmesartan, Olmesartan, Losartan (Angiotensin Receptor Blockers), Amlodipine (Calcium channel Blocker) and Atenolol, Metoprolol, Propranolol (β blocker)

STUDY METHODOLOGY

Study site
Study was conducted in Malla Reddy Health City, Narasapur Main Road, Suraram, Hyderabad, Telangana.
Study time
6 months (October 2016 – March 2017).

Inclusion criteria
- Age ≥18 years
- Grade 1 or 2 essential hypertension.
- Cardiovascular risk factors.
- Type 2 Diabetes.
- Three classes of anti-hypertensive drugs: Angiotensin Receptor Blockers β-Blockers Calcium Channel Blockers

Exclusion Criteria
- Shift workers.
- Heavy drinkers
- Heavy smokers (>20 cigarettes per day), and heavy exercisers were excluded, as were individuals with either severe arterial hypertension (grade 3, eg, BP ≥180/110 mm Hg).
- Type 1 diabetes and class II and class III obese patients (BMI ≥ 35).

Source Of Data
Patient case reports

Study Type
Prospective Study

METHODOLOGY PROCEDURE

Identify patients falling under inclusion criteria

Identify the antihypertensive medication administered to each patient

Collect specific background information (Demographic data, present medications, comorbidities)

Identify other medications given to the patient for comorbidities (eg. Hypoglycemics for Diabetes)
Measure blood pressure before administering antihypertensive medication (preferably before meal)

Compare the morning and bed-time fall in blood pressure after administration of the antihypertensive medication

This way we get two study populations (or) two cohorts.

Morning administration  Bed-time administration

Find out whether the medication administered for comorbidities affect the rise or fall in blood pressure.

RESULTS

- student t-test were used for calculating mean, ‘P’ value in the present study.
- In this study, 178 subjects who were on anti-hypertensive medication WERE RECRUITED. Treatment outcomes and safety parameters were assessed in the enrolled patients.
- Total number of individuals : 178.

1) Gender distribution among patients
Out of 178 hypertensive patients enrolled in the study, 58% i.e. 104 were males and 42% i.e. 74 were females. Males are predominantly prone to high blood pressure than females.

Table 1: distribution of gender.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>104 (58%)</td>
<td>74 (42%)</td>
</tr>
</tbody>
</table>
SOCIAL HISTORY
Hypertension was recorded mostly in alcoholics with 6.17%, followed by smokers with 10.67% and tobacco chewers were 5.05% among the patients.

Table 2: distribution according to social history.

<table>
<thead>
<tr>
<th>Social habits</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>19 (10.67%)</td>
</tr>
<tr>
<td>Alcoholics</td>
<td>9 (5.05%)</td>
</tr>
<tr>
<td>Tobacco chewers</td>
<td>11 (6.17%)</td>
</tr>
</tbody>
</table>

Fig 2: graphical data of social history.

2) MEDICAL HISTORY
- No. of patients with Diabetes(Type 1) : 0
- No. of patients with Diabetes(Type 2) : 53 (29.77%)
- No. of patients with CVA : 72 (40.4%)

Fig 1: distribution of patients based on gender.
Pranav et al.

Table 3: distribution of patients according to time of administration.

<table>
<thead>
<tr>
<th>ANTI-HYPERTENSIVE</th>
<th>No. of patients administered in MORNING (8:00am-10:00am)</th>
<th>No. of patients administered at BED-TIME (8:00pm-10:00pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB’s</td>
<td>73</td>
<td>11</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>57</td>
<td>4</td>
</tr>
<tr>
<td>CCB’s</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>

3) Distribution of patients based on time of administration. Out of 178 patients enrolled in the study, 73 patients were given ARB’s in morning, 11 patients were given ARB’s in evening, 57 patients were on β-blockers as morning treatment, 4 patients were given β-blockers as evening treatment, 14 patients were given CCB’s as morning treatment and 19 patients were given CCB’s as evening treatment.

4) Distribution of patients based on Anti-Hypertensive drugs given.

Table 4: distribution of patients based on Anti-Hypertensive drugs.

<table>
<thead>
<tr>
<th>Anti-hypertensive therapy</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANGIOTENSIN RECEPTOR BLOCKERS (TELMESARTAN, LOSARTAN, OLMESARTAN)</td>
<td>84 (47.19%)</td>
</tr>
<tr>
<td>BETA-BLOCKERS (ATENOLOL, METOPROLOL, PROPRANOLOL)</td>
<td>61 (34.26%)</td>
</tr>
<tr>
<td>CALCIUM CHANNEL BLOCKERS (AMLODIPINE, CLINIDIPINE)</td>
<td>33 (18.53%)</td>
</tr>
</tbody>
</table>

Fig 3: graphical representation of anti hypertensive drugs distribution.
This study depicted that the antihypertensive drug classes which are highly used in the study site show a significant fall in blood pressure. These classes may vary in the onset of action and half life respectively. In this study we covered three classes of anti-hypertensive drugs which are highly used in the hospital in which we were carrying out our study.

The anti-hypertensive classes which we covered in this study are Angiotensin Receptor Blockers, Calcium Channel Blockers, β-blockers.

The comparisons was made individually as follows.

- Comparisons of the systolic blood pressure when drug administered in the morning; comparison was made before administration and after administration of the drug and the same is done for the evening dose and then there is a cumulative comparison done so that there wuld be an accurate understanding of the drug effectiveness and chronological effect.
- On the other hand the comparison of the diastolic is done similar to that of systolic blood pressure. Comparing the diastolic BP separately when given or administered in the evening or in the morning.
- After the individual comparison the results are clubbed for the collective comparison.

MORNING VERSUS BEDTIME ADMINISTRATION

In this study 178 patients were enrolled are given with the medication as the morning daily doses and few are given the evening daily dose. Out of which among the three classes 73 patients were given ARB’s in the morning and patients were given as bed time doses, β-blockers were given to 57 patients as the morning doses whereas 4 patients were given as bed time dose.

On the other hand CCB’s were given to 14 patients as the morning doses and the.

Table 5: distribution of patients based on morning and evening dose.

<table>
<thead>
<tr>
<th>ANTI-HYPTERTENSIVE</th>
<th>No. of patients administered in MORNING (8:00am-10:00am)</th>
<th>No. of patients administered at BED-TIME (8:00pm-10:00pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB’s</td>
<td>73</td>
<td>11</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>57</td>
<td>4</td>
</tr>
<tr>
<td>CCB’s</td>
<td>14</td>
<td>19</td>
</tr>
</tbody>
</table>
remaining 19 patients were given as bed time doses.

The table above manifests the distribution of patients according to the time of administration of medication.

**The illustration of the results are as follows.**

**β-BLOCKERS**

- The most used β-blockers in our study site are atenolol, metoprolol, propranolol.
- Our study showed that Beta blockers showed little or no difference in the baseline blood pressure (systolic and diastolic) when administered in the morning or in the evening.
- Better 24-hour blood pressure was maintained when Beta blockers were administered as morning doses.
- The individual comparison of the drug administered are as follows.
  ✓ The administration of the β-blockers as the morning doses showed no significant difference in the systolic blood pressure.
  ✓ The mean of the systolic blood pressure was compared before the administration of the drug and after the administration of the drug.

The graphical data below gives an ease in understanding that the systolic blood pressure in the morning before the administration was to be 128.2 whereas after the morning dosing of the medication the systolic blood pressure was found to be 122.3.

Fig 4: Comparision of systolic blood pressure in the morning.
This exemplifies that there is no significant difference in the systolic blood pressure with morning dosing.

Advancing to β-blocker administered as the evening dose demonstrated that there is no convincing difference shown.

Much the same way of mean comparing is done for the evening doses.

Coming to the explanation of the graph the mean of the systolic blood pressure was found to be 128.2mmHg before administration while it was 122.3 mmHg after the administration.

This concludes that there is no suggestive significance in the systolic blood pressure when the β-blockers are administered in the evening.

![COMPARISON OF SYSTOLIC BP WHEN BETA-BLOCKER IS GIVEN IN THE EVENING](image)

**Fig 5: Comparison of systolic bp in the evening.**

The collective comparison of the systolic blood pressure when β-blockers are given as a morning dose and evening dose illustrates that there is no significant difference in fall of blood pressure when coming to morning blood pressure it was 128.2mmHg before administration and 122.2mmHg after administration on the other hand when medication was given as a evening dose the systolic blood pressure before administration was 122.3mmHg and was 122.35mmHg after administration.

The below graph gives a clear illustration if the cumulative comparison of systolic blood pressure which resulted in no significant difference in fall of blood pressure.
This study showed that β-blockers showed little or no difference in the baseline blood pressure (systolic and diastolic) when administered in the morning or in the evening.

The graph below illustrates comparison of the diastolic blood pressure. Diastolic blood pressure recorded before administration was 79.03mmHg and after administration was 78.03mmHg.

This proves to be no minimal change when the beta blockers are administrated in the morning.

On the other hand when β-blockers when administered as the evening doses there was little or no significant change in diastolic blood pressure.
The graphical representation below of the data that is been collected in the study site proves that similar to that of the morning dose there is no major difference when beta blockers are given as the evening dose.

The diastolic blood pressure was recorded to be 85mmHg that was before administration and which fell down to 81mmHg after administration. Thus, this proves to be that there no effective blood pressure fall of diastole.

![Fig 8: comparison of diastolic bp in the evening.](image)

The graph below shows the magnifying comparison between the diastolic blood pressures when β-blockers are given as the morning dose and as the evening doses and the data showed that there is no difference or mild difference from the baseline blood pressure.

![Fig 9: cumulative comparison of diastolic bp.](image)

The medication as the morning dose the diastolic blood pressure before administration was found to be 79.3mmHg whereas it was found to be 78.04mmHg after administration.
It was found similar to that of morning dose that there is no difference in fall of blood pressure which was 85mmHg before administration and 81mmHg before administration. Thus, there was no difference in fall of blood pressure significantly.

**ANGIOTENSIN RECEPTOR BLOCKERS**

In this study better 24-hour blood pressure was maintained when Angiotensin receptor blockers were given as morning or evening once daily doses. Also, Angiotensin receptor blockers had a little better effect in lowering blood pressure when administered in the evening versus when administered in the morning, though this was not significant.

On comparing the systolic blood pressure the ARB’s have shown mildly better effect in lowering blood pressure when administered in the morning.

The graph below shows that blood pressure was recorded as135.5mmHg before administration which fell down to 129.2mmHg after administration though wasn’t any considerable difference was not made.

![Comparison of systolic bp in the morning.](image)

On comparing the morning dose with that of the ARB’s given as the evening dose there was minute difference in fall of the systolic blood pressure.

As we can see in the graph below the systolic blood pressure was recorded to be 128.070mmHg which dipped to 1255.21mmHg after administration.

Thus, there was no significant difference illustration.
When coming to the cumulative comparison of the systolic blood pressure when ARB’s are given as morning dose to that of the evening dose. The data illustrated as the graphical representation in the graph below proves that the ARB’s show a better effect in the systolic blood pressure when administered as morning dose to that evening dose.

The ARB’s when given as the morning dose the diastolic blood pressure there was no great judging difference found as we can notice in the graph below the diastolic blood pressure before administration was found to be 84.5mmHg and then there was a minimal dip to 81.5mmHg of diastolic blood pressure. Thus, no differentiating dip of diastolic blood pressure.
When coming to the administration of ARB’s given as an evening dose the diastolic blood pressure alike to that of the morning dose even the evening dose of administration did not show any kind of considerable difference.

Advancing to the graph below the diastolic blood pressure before administration was 81.45mmHg and was 79.5mmHg after administration these leads to a conclusion that there is no considerable difference in diastolic blood pressure ARB’s as an evening dose.

On comparing the time of administration of ARB’s as the morning dose versus evening dose both the doses did not show any considerable desired difference in fall of the diastolic blood pressure.

The graph below gives the aggregate comparison of the diastolic blood pressure of both the morning dose and evening dose of ARB’s.
Thus, both the doses did not show any kind of the eye catching fall of the diastolic blood pressure.

Thus, we can come into a conclusion that ARB’s can be given either in as a morning dose or as an evening dose as they show the same minimal effect in dipping the diastolic blood pressure. Thus, when compared with the β-blockers ARB’s show a better circadian effect in lowering the blood pressure and this can be used over the β-blockers over a few conditions.

CALCIUM CHANNEL BLOCKERS
Calcium channel blockers significantly lowered the systolic blood pressure when administered in the evening than when administered in the morning. There were no significant changes seen in the diastolic blood pressure.

According to this study, Calcium channel blockers demonstrated better efficacy when administered at bed-time than when given as daily morning dose.

Better 24-hour blood pressure was maintained when Calcium channel blockers were administered as evening once daily doses than as morning once daily doses.

The graph below give u an ease explanation regarding the systolic blood pressure fall when calcium channel blockers(CCB) are administered as a morning dose.

Advancing to the graphical representation of mean of source data the systolic blood pressure recorded before administration of the calcium channel blocker it was 137.57mmHg after administration it was recorded as 131.01mmHg.
Thus, this makes us conclude that there is no major difference alike the other two class when administered as the morning dose.

![Fig 16: comparison of systolic bp.](image1)

Progressing to the graphical representation of the systolic blood pressure when calcium channel blockers are given as evening dose there was an extensive difference seen in the systolic blood pressure.

The systolic blood pressure which was recorded before the administration was 136.23mmHg which miniaturised to 127.88mmHg.

Thus, on this we can relay that calcium channel blockers showed a lowering of systolic blood pressure when administered as an evening dose.

![Fig 17: Comparison of Systolic bp.](image2)
Preceding to the diastolic blood pressure as such of systolic blood pressure there was no notable difference in fall of blood pressure as before administration it was noted as 88.11mmHg when after administration it was 82.14mmHg. Thus, there was no considerable change in fall of the diastolic blood pressure.

![Comparison of diastolic BP when CCB's are given in the morning](image)

**Fig 18: comparison of diastolic bp.**

On the contrary there was a similar nature in diastolic blood pressure when calcium channel blockers are administered as an evening dose there was eye catching difference seen.

When the CCB’s are administered as an evening dose the diastolic blood pressure was noted as 87.02mmHg and after administration if was found to be 81.56mmHg.

Thus, in the same manner of the morning dose there was no considerable difference.

![Comparison of diastolic BP when CCB’s are given in the evening](image)

**Fig 19: comparison of diastolic bp.**
Amass comparison of the systolic blood pressure when CCB’s administered as a morning dose versus evening dose which lead to clear conclusion that CCB’s give an effective fall in systolic blood pressure when administered as an evening dose rather than the morning dose. The graph below gives a pictorial representation of the data which gives the conclusion that it lead us.

![Cumulative comparison of systolic BP](image)

**Fig 20:** cumulative comparison of systolic bp.

When on the other hand there was no significant or considerable difference when aggregate comparison of the diastolic blood pressure was done. It was same as such when CCB’s given as a morning dose or as an evening dose the graph below gives u and ease in understanding the fall in diastolic blood pressure.

![Cumulative comparison of diastolic BP](image)

**Fig 21:** cumulative comparison of diastolic bp.
CONCLUSION

Most patients were prescribed with Angiotensin receptor blockers (84 patients), followed by Beta blockers (61 patients) and Calcium channel blockers (33 patients).

In this study which was done in the study site that was Malla Reddy Health City lead us to conviction that β blockers showed little or no difference in the baseline blood pressure (systolic and diastolic) when administered in the morning or in the evening.

Also, Angiotensin receptor blockers had a little better effect in lowering blood pressure when administered in the evening versus when administered in the morning, though this was not significant.

Calcium channel blockers significantly lowered the systolic blood pressure when administered in the evening than when administered in the morning. There were no significant changes seen in the diastolic blood pressure. According to this study, Calcium channel blockers demonstrated better efficacy when administered at bed-time than when given as daily morning dose. When compared to Calcium channel blockers, β-blockers and Angiotensin receptor blockers showed better efficacy when administered as morning doses.

Diastolic BP is more important in assessing Cardiovascular risk in people aged younger than 40 years. Systolic blood pressure is recognised as an important measure for the risk of developing stroke and heart failure in patients aged above 40 years. Controlling systolic BP decreases the risk of developing Cardiovascular diseases in elderly patients. However, current evidence suggests that over the age of 40 years, Systolic BP holds more importance and under the age of 40 years, Diastolic BP is of high importance.

DISCUSSIONS

❖ According to Hermida et al. the once daily evening, in comparison to morning, ingestion schedule of the ARB significantly improved the sleep time- relative BP decline in hypertensive patients also observed in this study where ARB’s had a mildly better effect in lowering blood pressure when administered in the evening when compared to morning administration, though this was not significant.

❖ According to Zappe et al. once-daily dosing of ARB results in equally effective 24-h BP efficacy, regardless of dosing time which is in harmony to this study that shows no significant changes in morning vs bedtime dosing of ARB’s
According to Hermida et al. Telmesartan administered at bedtime, as opposed to morning dosing, improved the sleep time-relative blood pressure decline toward a more dipper pattern without loss in 24-hour efficacy which corresponds to our study.

According to Qiu et al. morning administered amlodipine had a better effect on the circadian BP compared with evening administrated amlodipine in mild-to-moderate essential hypertension, in contrast to this study where nocturnal BP regulation was significantly achieved with bedtime dosing of amlodipine.

This study showed that Beta blockers showed little or no difference in the baseline blood pressure (systolic and diastolic) when administered in the morning or in the evening.

Calcium channel blockers significantly lowered the systolic blood pressure when administered in the evening than when administered in the morning. There were no significant changes seen in the diastolic blood pressure.

According to this study, Calcium channel blockers demonstrated better efficacy when administered at bed-time than when given as daily morning dose.

When compared to Calcium channel blockers, beta blockers and angiotensin receptor blockers showed better efficacy when administered as morning doses.

According to Kaur G. et al, better 24-hour blood pressure was maintained when Beta blockers were administered as morning doses correlating to the present study.

Better 24-hour blood pressure was maintained when Angiotensin receptor blockers were given as morning or evening once daily doses.

Better 24-hour blood pressure was maintained when Calcium channel blockers were administered as evening once daily doses than as morning once daily doses which correlated to the results of White et al.

In order to imprecise daytime and night-time dosing periods, we used narrower windows for the morning (8 a.m. to 10 a.m.) and night-time (8 p.m. to 10 p.m.) periods.

If the anti-hypertensive medication is given once daily there should be at most care to be taken in maintaining the controlled blood pressure for the whole circadian blood pressure until the next dosing interval.

FUTURE DIRECTIONS

More studies on the relationship between chronology and circadian rhythm on blood pressure and blood pressure medications need to be done.
For a better assessment regarding the chronological effect of anti hypertensive drugs on the body a much of huge sample is to be considered. This enormous sample consideration may help in proper usage of the drug.

Along with the gigantic sample consideration there blood pressure monitoring taken under consideration along with measuring the drug levels in the blood during day time and night time.

REFERENCES


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