Comparison of efficacy and safety of olmesartan and hydrochlorothiazide with telmisartan and hydrochlorothiazide in patients with mild to moderate hypertension

By

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DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

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April 2015

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I hereby declare that this dissertation entitled **"COMPARISON OF EFFICACY AND SAFETY OF OLMESARTAN AND HYDROCHLOROTHIAZIDE WITH TELMISARTAN AND HYDROCHLOROTHIAZIDE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA. N,** Professor and HOD, Department of Pharmacology Sri Devaraj Urs Medical College, Tamaka, Kolar.

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This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **Dr. REVATHI RAMESH**, a postgraduate student in the Department of Pharmacology of Sri Devaraj Urs Medical College entitled "**COMPARISON OF EFFICACY AND SAFETY OF OLMESARTAN AND HYDROCHLOROTHIAZIDE WITH TELMISARTAN AND HYDROCHLOROTHIAZIDE IN PATIENTS WITH MILD TO MODERATE HYPERTENSION"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar.

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"When we give cheerfully and accept gratefully, everyone is blessed."
Maya Angelou

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Place: Kolar **Dr. REVATHI RAMESH**

Dedicated with

Reverence

to

My Parents

LIST OF ABBREVIATIONS

WHO	World Health Organization
JNC 8	Joint National Committee 8
BP	Blood pressure
HCTZ	Hydrochlorothiazide
RAAS	Renin Angiotensin Aldosterone System
ARB	Angiotensin receptor blocker
AT_1	Angiotensin-1 receptor
NO	Nitric Oxide
ANP	Atrial Natriuretic Peptide
ACE	Angiotensin Converting Enzyme
A-I	Angiotensin I
A-II	Angiotensin II
G_q	G_q coupled receptor
PLC	Phospholipase C
IP_3	Innositol-3-Phosphate
Ca^{2+}	Calcium
Na^+	Sodium
K^+	Potassium
H^+	Hydrogen
Cl^-	Chloride
HCO_3^-	Bicarbonate
GFR	Glomerular filtration rate
TGF-β	Transforming growth factor β
PDGF	Platelet derived growth factor
PPAR γ	Peroxisome proliferator activated receptor γ

TNF-α	Tumour necrosis factor α
IL-6	Interleukin 6
CRP	C-reactive protein
CGRP	Calcitonin gene-related peptide
Cmax	Peak plasma concentration
AUC	Area under the curve
NSAID	Non-steroidal anti-inflammatory drugs
GLUT4	Glucose transporter type - 4
ATP	Adenosine triphosphate
ACTH	Adrenocorticotropic hormone
FBS	Fasting blood sugar
PPBS	Post prandial blood sugar
ANOVA	Analysis of variance
ADRs	Adverse drug reactions

ABSTRACT

Background

Hypertension is one of the most prevalent non communicable diseases. JNC VIII guidelines recommend angiotensin receptor blockers (ARBs) as the first line drug and addition of hydrochlorothiazide (HCTZ) increases their efficacy. Olmesartan medoxomil is a recently introduced, whereas Telmisartan is a relatively older ARB.

Objectives

1. To study the efficacy of olmesartan and hydrochlorothiazide in the treatment of mild to moderate hypertension-Joint National Commission (JNC) VIII

2. To compare the efficacy of olmesartan and hydrochlorothiazide with telmisartan and hydrochlorothiazide in the control of hypertension

3. To study the safety profile of the above drug combinations

Materials and methods

This study was conducted on patients presenting to the Department of Medicine, R.L. Jalappa Hospital and Research Centre. 120 Patients clinically diagnosed with mild to moderate hypertension were randomly divided into two groups. They received either olmesartan 20mg+HCTZ12.5mg (GpO) or telmisartan 40mg+HCTZ12.5mg (GpT) orally once daily for 8 weeks.

Blood pressure and heart rate were recorded at baseline, 4th and 8th week. Laboratory investigations like fasting blood glucose (FBS), post prandial blood glucose(PPBS), lipid profile, serum electrolytes and routine urine examination were done at baseline and repeated at the end of 8th week. The patients were advised to report any adverse events as and when they occurred

Interpretation and Results

Fourty six (GpO) and fourty four (GpT) patients completed the study. Majority of patients were in 5th decade of life (72.3%), 56% were males, 35% had type II diabetes mellitus and received oral antidiabetics. The mean BP was 148.6±5.9/ 89.2±5.9 and 147.9±5.2/ 88.1±4.2 mmHg at baseline and decreased significantly at week 8 to 131.0±5.4/ 80.3±2.9 and 136.8 ±5.5/ 83.6±3.9 mmHg in GpO and GpT respectively. Patients in GpO had significant reduction in systolic BP (SBP)(p=0.0001) and diastolic BP (p=0.04) than GpT. More than 10mmHg decrease in SBP was observed in 86.9 Vs 65.9% of patients in GpO and GpT which was significant (p=0.01). Diabetic patients in both groups had a significant decrease in blood sugar by week 8 but intergroup comparison was insignificant. Change in heart rate and lipid profile was negligible. Common adverse effects were dizziness, abdominal pain and pedal edema in both groups.

Conclusion: Olmesartan+HCTZ was more effective than telmisartan+HCTZ in lowering BP .

Key words: Hypertension, olmesartan, telmisartan , hydrochlorothiazide

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Introduction

Introduction

According to the WHO 2012 statistics, it was found that 63% of annual deaths were due to non-communicable diseases of which cardiovascular deaths accounted for 48%. Hypertension being the most common cause of cardiovascular disease. In 2000 it was estimated that nearly 1 billion adults suffered from hypertension and this number is expected to rise to 1.5 billion by 2025.[1,2] Presently in India the prevalence of hypertension is 25% in urban and 10-15% among rural adults.[3] Hypertension is associated with impaired- kidney sodium excretion, plasma volume, cardiac output and vascular tone. Alterations in the renin-angiotensin- aldosterone system and sympathetic nervous system play a role in the development of hypertension.

The eighth report of the joint national committee (JNC 8) provides new guidelines for the prevention, detection and treatment of high blood pressure (BP). The main goal of therapy is to effectively control blood pressure in order to avoid or postpone the development of complications. Patients should be advised to adopt lifestyle modifications such as healthy diet, weight control, smoking cessation and regular exercise. Emphasis on patient education must be made and they should be instructed that drug treatment is generally lifelong and compliance is important.[4]

BP elevation is usually multi factorial and more over compensatory mechanisms make monotherapy ineffective, as high doses of the drug are required to control it. These doses are also associated with an increased incidence of adverse effects. Therefore combination therapy is superior to monotherapy in the treatment of hypertension.[5] The synergistic action of two antihypertensive drugs from different classes has been shown to benefit the patient profoundly, in terms of effective reduction in blood pressure and minimizing the side effects due to each individual drug.

Thiazide diuretics such as hydrochlorothiazide (HCTZ) have been first-line antihypertensive drugs for several years. It is known that, they open potassium channels in the vascular smooth muscles and cause vasodilatation, thus resulting in fall in BP. This fall will activate the Renin angiotensin aldosterone system (RAAS). A high level of RAAS activity is needed for optimal blockade by angiotensin receptor blocker (ARB). Thus the reduction in BP obtained by the combination of HCTZ and ARB is higher than the reduction from the use of either drug alone.[6]

Olmesartan medoxomil is a recently introduced ARB, it is a pro-drug that is converted into olmesartan in the body. Olmesartan has specific affinity for angiotensin-1 receptor (AT_1) in the vasculature. Once bound to the receptor it dissociates very slowly. The initial binding to the receptor is loose or 'surmountable' this is then followed by the development of a tighter or 'insurmountable' binding. Due to this unique mode of action, olmesartan has been found to have improved efficacy.[6] Telmisartan is a relatively older ARB. Its efficacy in reduction of BP has been well established. In the Indian population, there is paucity of information regarding the comparison of fixed dose combination of olmesartan + HCTZ and telmisartan + HCTZ, in terms of efficacy and safety in reducingBP. Hence this study was undertaken.

Objectives

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Review

Of

Literature

Review of literature

History of hypertension

In 2600 BC: acupuncture, venesection and bleeding by leeches were used to treat hypertension which was then called 'hard pulse disease'. Emperor of China Chou You, Celsus, Galen, and Hippocrates all indorsed venesection.[7]

In the 1940s: thiocyanates, barbiturates, bismuth, and bromides were used as supportive measures along with lifestyle modifications—rest and avoidance of stress. Dr. Edward D. Freis, used the antimalarial agent pentaquine for the treatment of malignant hypertension. Sympathectomy and adrenalectomy were also performed on hypertensives. [8]

In the 1950s: Phenoxbenzamine, hexamethonium, pentolinium, mecamylamine, guanethidine, reserpine and hydralazine were discovered. They were all highly effective in reducing BP, but side effects and adherence to therapy were major problems.[9] A major breakthrough in the treatment of hypertension that took place during this era is the discovery of chlorothiazide. This new drug was efficacious and well tolerated, it was found to reduce the morbidity and mortality associated with the disease and prolonged life expectancy in these patients.[10]

In the 1960's-1990: beta blockers were introduced into clinical practice during the 1960's. Propranolol being the first in its class, followed by more cardioselective agents. In 1977, the first report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC I) was published.[11] According to its recommendations, no action was needed unless the diastolic BP was ≥105 mm Hg. The emphasis in JNC I was on treating the diastolic pressure. No guidelines were provided for the staging of hypertension based on

systolic pressure. During this period calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were developed.

21st century: modern approach to the treatment of hypertension is based on the guidelines and recommendations of the joint national committee VIII. Well defined targets for blood pressure control have been established. (<130/80 mmHg). The percentage of patients meeting these targets has increased in recent years, with the advent of newer more efficacious antihypertensive drugs. [12]

History of ARBs

Physiologist Robert Tigerstedt in 1898 conducted experiments on rabbits and proposed that the kidneys produced 'renin' that caused a rise in blood pressure.[13] In the 1930s, Goldblatt experimented on dogs, where he constricted the renal blood vessels and discovered that ischemic kidneys secreted a chemical that caused vasoconstriction. In 1939, renin was found not to cause the rise in blood pressure, but was an enzyme which catalyzed the formation of angiotensin I and II. It was later observed individuals with high levels of renin activity had a higher risk of adverse cardiovascular events like myocardial infarction and stroke.[14]

In 1980s it was observed that imidazole-5-acetic acid derivatives: S-8307 and S-8308 were found to diminish blood pressure responses to angiotensin II in rats. Structural modifications were made and AT_1 receptor blocker losartan was developed.[15] In 1995 losartan was approved for clinical use in the United States. Since then a number of angiotensin receptor blockers have been used, these include valsartan, candesartan, irbesartan, telmisartan, azilsartan, and olmesartan.

History of thiazide diuretics

In the 20th century, Alfred Vogel a Viennese medical student observed that patients passed large amounts of urine after receiving organomercurial compounds for treatment of syphilis. Subsequently they were used as diuretics, however their prolonged use resulted in toxic side effects.

By the late 1950s, thiazide diuretics were developed by scientists at Merck, hydrochlorothiazide became very popular in the treatment of edema and congestive heart failure and hypertension.[16]

Etiological factors of hypertension

Essential hypertension, or hypertension of unknown cause, accounts for more than 90% of hypertensive patients. It has a multifactorial etiology

A. *Genetic factors* : Population studies have shown familial trends in hypertension.[17-19] These genetic factors may be carried on a single gene (monogenic) or on multiple genes (polygenic). Monogenic forms - glucocorticoid- remediable aldosteronism, Liddle's syndrome, apparent mineralocorticoid excess, autosomal dominant hypertension with brachydactyly. Polygenic forms - angiotensinogen gene, angiotensin converting enzyme (insertion/deletion), aldosterone synthase, alpha adducin ,G protein β_3 subunit nitric oxide generation, Na^+ Li^+ counter transport, epithelial amiloride sensitive sodium channel[20]

B. *Fetal factors*: Intrauterine growth restriction inhibits formation of adequate nephrons, impairs angiogenesis, and causes increase in inflammatory cytokines and expression of metabolic genes. Glucocorticoid exposure in utero increases production of reactive oxygen species, and impairs development of nephrons. These factors lead to the development of hypertension in adults.[21]

C. *Environmental factors* : The risk factors for hypertension include- obesity, excessive alcohol intake, increased salt intake, smoking, psychological stress, low physical activity

D. *Insulin resistance*: Diabetes and hypertension are closely related. Insulin resistance leads to increased renal sodium reabsorption, activation of the sympathetic nervous system, alteration of transmembrane ion transport, and hypertrophy of resistance vessels and can thus lead to the development of essential hypertension.[22]

Pathophysiology of hypertension

Vascular remodeling: Arteriosclerosis results from collagen deposition, smooth muscle hypertrophy and fragmentation of elastin fibers in the tunica media-leading to narrowing of the lumen, thus leading to increase in peripheral vascular resistance and rise in BP.

Sympathetic nervous system: hypertensives have an exaggerated chemoreceptor reflex function, leading to excessive sympathetic activation in response to stimuli such as apnea and hypoxia. Chronic sympathetic stimulation induces vascular remodeling and left ventricular hypertrophy, by actions of norepinephrine, transforming growth factor- β, insulin-like growth factor 1, and fibroblast growth factors.

Endothelial dysfunction and vasoactive substances: Nitric oxide (NO) is a potent vasodilator, inhibitor of platelet aggregation, suppressor of migration of leucocytes and proliferation of vascular smooth-muscle cells. NO is diminished in hypertensive persons. Endothelin (vasoactive peptide) acts on smooth-muscle cells to cause vasoconstriction and elevate blood pressure. Circulating endothelin levels are increased in hypertensive patients. Atrial Natriuretic Peptide (ANP) – is secreted by the atria in response to increased blood volume. Deficiency of ANP leads to fluid retention and rise in blood pressure.[23]

Renin–angiotensin–aldosterone system (RAAS): plays an essential role in the regulation of blood pressure.

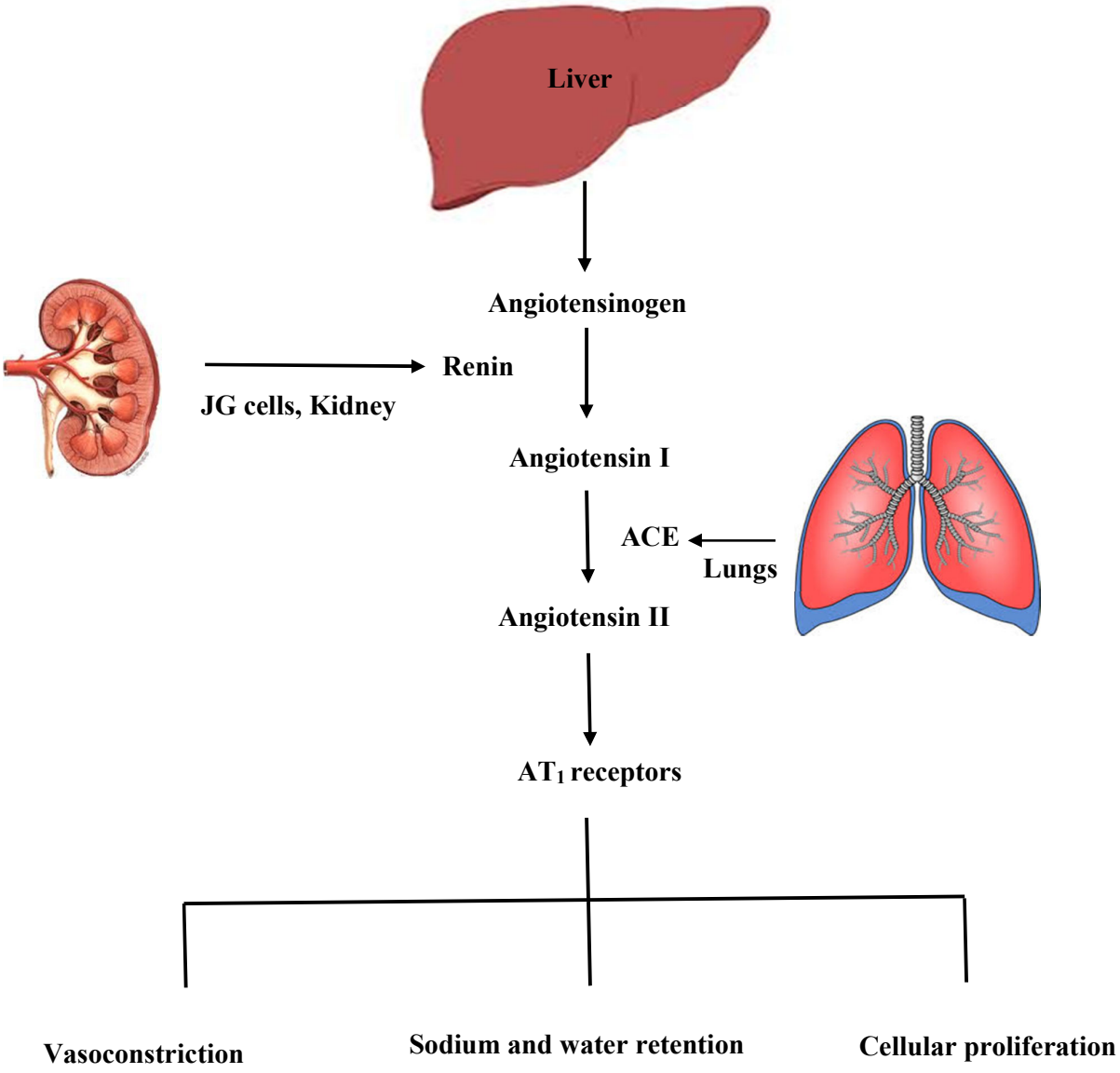

Figure 1. The renin angiotensin aldosterone system

Angiotensinogen can be converted to angiotensin I (A-I) by nonrenin enzymes such as tissue plasminogen activator, cathepsin G, elastase, and chymostatin, and A-I can be converted to angiotensin II (A-II) by non-ACE enzymes such as chymostatin-sensitive A-II–generating enzyme, chymase, and cathepsin G.[28]

AT_1 receptors are located on the *vascular smooth muscle* cells of arterioles, their stimulation results in activation of G_q-PLC-IP_3-Ca^+ pathway. Which in turn brings about vasoconstriction, increase in peripheral vascular resistance and hence BP. In addition, A-II also enhances peripheral noradrenergic neurotransmission, central sympathetic discharge and causes release of catecholamines from the adrenal medulla. All these mechanisms result in the '*rapid pressor response*' and cause a rise in blood pressure. Angiotensin II has a major effect on *renal functions*. It acts directly on the Na^+/H^+ transporter and the Na^+-K^+-$2Cl^-$ symporter and enhances the reabsorption of Na^+ from the proximal tubule and the thick ascending limb of the loop of Henle. It stimulates the zona glomerulosa of the adrenal cortex to secrete aldosterone which in turn results in increased Na^+ reabsorption and K^+ excretion from the distal nephron. The net effect results in fluid electrolyte retention and rise in blood pressure. Renal hemodynamics are also altered, constriction of afferent arterioles reduces glomerular filteration rate (GFR). This leads to rise in plasma volume and increase in pre load which in turn increases blood pressure. The above mentioned effects of A-II contribute to the '*slow pressor response*' which is responsible for the long term rise in blood pressure produced by the activation of the renin angiotensin aldosterone system.[29]

On vascular and cardiac hypertrophy and remodeling, A-II induces the expression of proto-oncogenes (c-fos, c-jun etc) which causes an increased expression of growth factors such as TGF-β, PDGF etc. As a result, hypertrophy and hyperplasia

of smooth muscle cells, cardiac myocytes and fibroblasts occurs. Increase in preload (due to fluid and electrolyte retention) and afterload (peripheral vasoconstriction) also facilitates hypertrophy and hyperplasia in the heart.

Blockade of the AT_1 receptor inhibits generalized cellular proliferation and hypertrophy, thereby antagonizing the trophic responses in tissue induced by A-II.[29]

JNC VIII report

In December 2013, the Joint National Committee VIII announced the revised guidelines for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure in order to help clinicians in managing hypertension in adults. The guidelines provided are based on the evidence of randomized control trials and expert opinions.[26,27]

Table 1. Classification of hypertension – JNC VIII

Category	Systolic BP mmHg		Diastolic BP mm Hg
Normal	<120	And	<80
Pre hypertension	120-139	Or	80-89
Stage I hypertension	140-159	Or	90-99
Stage II hypertension	>160	Or	>100

Table 2. Criteria for initiating drug therapy – JNC VIII

Age – years	Systolic BP mm Hg		Diastolic BP mm Hg
<60	140	Or	90
>60	150	Or	90

Table 3. Initial drug-class choices – JNC VIII

Non Black	Thiazide diuretics, calcium-channel blockers, angiotensin-converting–enzyme inhibitors, or angiotensin-receptor blocker
Black	Thiazide diuretics or calcium channel blockers
Patients with chronic kidney disease	angiotensin-converting–enzyme inhibitors, or angiotensin-receptor blocker

OLMESARTAN

Olmesartan medoxomil is an AT_1 receptor antagonist. It has more than 10,000-fold greater affinity for the AT_1 than for the AT_2 receptors. It blocks all actions of angiotensin II mediated by the AT_1 receptor, irrespective of the source of synthesis of angiotensin II. The initial binding of olmesartan is loose "surmountable" followed by a tighter, "insurmountable" binding complex.

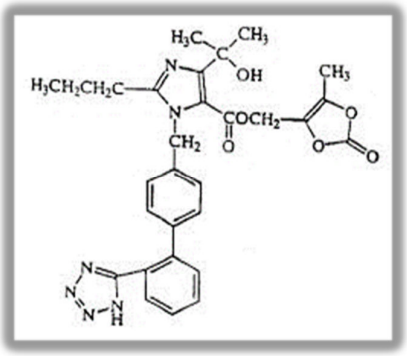

Figure 2. Structure – olmesartan[28]

Olmesartan causes a dose-dependent reduction in blood pressure by antagonizing the actions of A-II at various sites (Figure1). There has been no evidence of first-dose hypotension, tachyphylaxis during long-term treatment, or rebound hypertension after termination of therapy. Substantial reduction in BP is observed after initial 2 weeks of treatment.[28]

Other actions of olmesartan

This drug induces PPAR γ which functions as a transcriptional regulator of multiple genes involved in glucose and lipid metabolism, this pleiotropic action offers antidiabetic effects.[24] Hypertensive patients are reported to have high circulating

levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). Olmesartan lowers these inflammatory cytokines and is therefore found to possess anti-inflammatory and antioxidative properties.[25]

Circulating endothelial progenitor cells and calcitonin gene-related peptide (CGRP) levels increase following the administration of olmesartan. Studies show that injured vascular endothelium is repaired via circulating endothelial progenitor cells and that CGRP prevents and reverses A II-induced cell senescence. Hence it can be concluded that this drug has anti-atherosclerotic properties.[32]

Through these various actions, olmesartan not only lowers blood pressure but also prevents remodeling of the heart and blood vessels and thereby delays the progression of heart failure[30,31], decreases the incidence of sudden death and myocardial infarction in all patients.[32]

Pharmacokinetics

Olmesartan medoxomil is a prodrug converted to active metabolite, olmesartan, by esterases in the gut mucosa and in portal blood. It has an oral bioavailability of 25.6% and food has negligible effect on this. Mean peak plasma concentration (Cmax) is reached within 2 hours after oral administration. The volume of distribution is in the range of 16–29 liters, with 99.7% plasma protein binding, (however this drug does not cause significant interactions). The binding to blood cells is negligible and it crosses the blood-brain barrier poorly. Animal experiments reveal that it can cross the placental barrier and appear in breast milk.

There is nearly no further metabolism of olmesartan. It has a total plasma clearance is 1.3 L/h and a Renal clearance of 0.5– 0.7 L/h independent of dose.

Approximately 30% to 50% of the systemically absorbed drug is excreted in urine and the remainder in faeces (via the bile). Steady stat is reached after the first few doses and no further accumulation is evident after 14 days of repeated dosing.

In elderly (65–75years) the Area under the curve (AUC) at steady state was increased (33%) compared with the younger age group. Patients with renal insufficiency (creatinine clearance <30mL/min) and moderate hepatic impairment (Child-Pugh score 7 - 9) AUC increased significantly. Therefore caution must be exercised and dose reduction done where necessary.

Indication - Treatment of hypertension.

Contraindications - Patients who are hypersensitive to olmesartan medoxomil , severe renal impairment (creatinine clearance <30 mL/min), severe hepatic impairment (Child-Pugh score 10 - 15) or biliary obstruction and pregnancy.

Table 4. Drug Interactions - olmesartan

1.Potassium supplements, potassium sparing diuretics and other drugs that may increase serum potassium levels (e.g. heparin)	Increases serum potassium
2.Non-steroidal anti-inflammatory drugs (NSAIDs) at doses >3 g/day	Decreases glomerular filtration
3.Antacid (aluminium magnesium hydroxide)	Reduction in bioavailability
4. Lithium	Reversible increase in serum lithium concentration

➢ Fatigue	➢ Insomnia
➢ Headache	➢ Rash
➢ Influenza-like symptoms	➢ Diarrhea,
➢ Peripheral edema	➢ Vomiting
➢ Dizziness and drowsiness,	➢ Bronchitis
➢ Insomnia	➢ URTI

Table 5. Adverse effects - olmesartan (incidence 1-10%)

Dosage and formulation : It is available for oral use as film-coated tablets containing 10 mg, 20 mg, or 40 mg olmesartan medoxomil.

TELMISARTAN

Telmisartan is a lipophilic, highly selective, AT_1 receptor antagonist, which dissociates slowly once bound to the AT_1 receptor thereby contributing to its duration of action.[36] Its efficacy and safety has been well established for the treatment of hypertension.

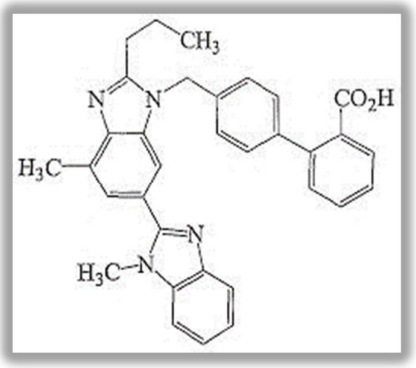

Figure 3. Structure – telmisartan [37]

This drug interacts with the PPAR-γ receptor, which is a nuclear transcription factor involved in carbohydrate and lipid metabolism. Telmisartan acts as a partial agonist of PPAR-γ at therapeutic doses in contrast to other ARBs.[37] Telmisartan also reduces glucose and triglyceride levels and increases glucose uptake and GLUT4 expression, factors that may translate into a favourable metabolic profile [38]

Pharmacokinetics: Telmisartan is rapidly absorbed from the gastrointestinal tract. The approximate bioavailability of telmisartan is 43%, volume of distribution - 500 L (highest of all ARBs) , elimination half-life -~24 hours, (longest). These properties ensure sustained antihypertensive effect. Steady state plasma concentration is achieved within 7 days. Telmisartan is metabolised by glucuronide conjugation , and the resultant metabolite has no pharmacological activity. Excreted largely unchanged in the faeces, via biliary excretion; <1% is excreted in the urine.[39]

Safety and tolerability : Telmisartan is associated with relatively few side- Headach, upper-respiratory tract infection, fatigue, diarrhoea, back pain, dizziness, dyspepsia and rashes.[40] Rarely discontinuation due to adverse events occurred in patients taking telmisartan compared with placebo (2.8 vs 6.1%)

HYDROCHLOROTHIAZIDE

Mechanism of action

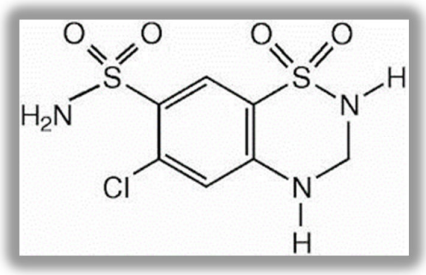

Figure 4. Structure – hydrochlorothiazide [41]

Hydrochlorothiazide binds to the Na^+Cl^- symport present on the luminal surface of the cells of the distal convoluted tubule and inhibits re absorption of these electrolytes.

This class of diuretics is termed as 'moderately efficacious as >90% of the filtered Na^+ is reabsorbed at the proximal convoluted tubule and Loop of Henle. It is also a weak inhibitior of carbonic anhydrase (HCO_3^- and phosphate excretion). The most significant action of this drug in lowereing blood pressure on a long term basis is due to the vasodilation it produces by binding to the ATP sensitive K^+ in the peripheral blood vessels. Other less important actions include: inhibition of - cyclic nucleotide phosphodiesterases, mitochondrial o_2 consumption and renal uptake of fatty acids.[41]

Pharmacokinetics

Following oral administration Hydrochlorothiazide is well absorbed (bio availability - 75%, with food- 65%). Absorption is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing. It is 40% plasma protein bound and has an elimination half-life of around 4 hours. It is excreted primarily (95%) in urine.[42]

Adverse effects : weakness, hypotension,gastro intestinal disturbances such as diarrhea, vomiting, cramping, constipation, gastric irritation, nausea and anorexia. Hyperuricemia or acute gout may be precipitated in certain patients receiving thiazide diuretics. Calcium excretion is decreased by thiazides, and pathologic changes in the parathyroid glands, with hypercalcemia and hypophosphatemia, have been observed. Some of the rare but serious drug related effects include aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia and thrombocytopenia

Drug interactions

i. Alcohol, barbiturates, or narcotics – increases incidence of orthostatic hypotension.
ii. Antidiabetic drugs- (oral agents and insulin)- thiazides decrease the efficacy of these drugs.
iii. Cholestyramine and colestipol resins - Cholestyramine and colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43% respectively.
iv. Corticosteroid, ACTH - intensifies hypokalemia
v. Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - increased responsiveness to the muscle relaxant
vi. Lithium - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity
vii. Non-steroidal anti-inflammatory drugs - the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of thiazide diuretics.
viii. Thiazides increase the the risk of Torsades de pointes produced by quinidine by causing hypokalemia

Safety and efficacy in pediatric patients has not been established. A greater blood pressure reduction and an increase in side effects may be observed in the elderly (i.e.,

> 65 years) with hydrochlorothiazide, hence it is recommended that therapy should be started with a low dose.In case of impaired hepatic function: Thiazides should be used with caution as they can precipitate hepatic coma. [43]

Indications

1. Essential hypertension
2. Treat edema associated with : Congestive heart failure, hepatic failure, nephrotic syndrome, glomerulonephritis
3. Calcium nephrolithiasis
4. Nephrogenic diabetes insipidus

Contraindications

1. GFR<30ml/min
2. Hypersensitivity to the drug

Dosage and administration

For control of hypertension: The adult initial dose of 12.5 mg-25mg hydrochlorothiazide. Total daily doses greater than 50 mg are not recommended.[44-45]

Materials

and

Methods

Materials and Methods

This study was conducted from January 2013 to June 2014 in patients clinically diagnosed with hypertension. A total of 120 patients were recruited for the study.

Location of study: The study was conducted on outpatients attending the Department of Medicine at R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Data collection: A proforma containing detailed information of each patient was designed according to the study protocol. Ethical clearance was obtained from Institutional Ethics Committee. Patients who were willing to give the written informed consent were included in the study.

Inclusion Criteria:

1. Patients of either gender, aged between 30-70years
2. Patients with mild to moderate hypertension as per JNC VIII (BP >140/90mmHg)
3. Patients with diabetes mellitus (type II) on oral antidiabetic drugs

Exclusion Criteria:

1. Patients with severe hypertension (BP>160/100mmHg)
2. Renal or hepatic dysfunction
3. Hypersensitivity to the test drugs
4. Pregnancy or lactation

Method of collection of data:

Patients clinically diagnosed with mild to moderate hypertension were included in the study. They were randomly divided into two groups to receive either olmesartan 20mg + HCTZ 12.5mg (GpO) or telmisartan 40mg + HCTZ 12.5mg (GpT) orally once daily for 8 weeks.

Relevant data was collected from the patients. This included name, age, occupation, history of present illness, past history and family history of the patients. A general physical examination was done, vital signs like blood pressure, heart rate, respiratory rate, peripheral pulses were recorded. Systemic examination of cardiovascular, respiratory, abdominal and central nervous system was done. Patients were asked to come for follow up at the 4^{th} and 8^{th} week.

The blood pressure was measured in the sitting posture using a standard mercury sphygmomanometer at baseline, 4^{th} week and 8^{th} week. Laboratory investigations like fasting blood glucose (FBS), post prandial blood glucose (PPBS), lipid profile and serum electrolytes were assessed at baseline and repeated at the end of 8^{th} week.

The patients were advised to report any adverse events as and when they occurred. These events were documented and assessed in accordance with the WHO causality assessment scale. The events were classified as-

Certain : if it has a plausible time relationship to drug intake and if the adverse effect subsided on withdrawing the drug and if on re challenge it reoccurs

Probable: if it has a reasonable time relationship to drug intake, if adverse effect subsides on withdrawing the drug

Possible: if it has a reasonable time relationship to drug intake if adverse effect can be explained by disease or other drugs

Unlikely: if it has an improbable time relationship to drug intake, if the adverse effect can be explained by disease or other drugs

Conditional : if more data for assessment is required

Unassessable : if data cannot be supplemented or verified

If intolerance occurred, drug was stopped and alternative treatment was initiated.

Statistical methods:

Taking into consideration a power of 80% and an α error of 5% to detect a difference of 3.2 mm Hg in the diastolic blood pressure in 8 weeks, with an effect size of 0.64 and a drop out rate of 10%, the sample size was calculated to be 42 patients per group. The demographic data was analysed using descriptive statistics. The blood pressure values of the two groups were compared using unpaired t test, paired t test and repeated measure ANOVA. The FBS, PPBS, lipid profile and serum electrolytes was compared using the unpaired t test. Adverse effects analysed using the Chi Square test. A p value of <0.05 was considered to be statistically significant.

Results

Results

Patients recruited in our study were 120 but 90 patients completed the eight week study period (Figure 5). Analysis was done for patients who have completed the study.

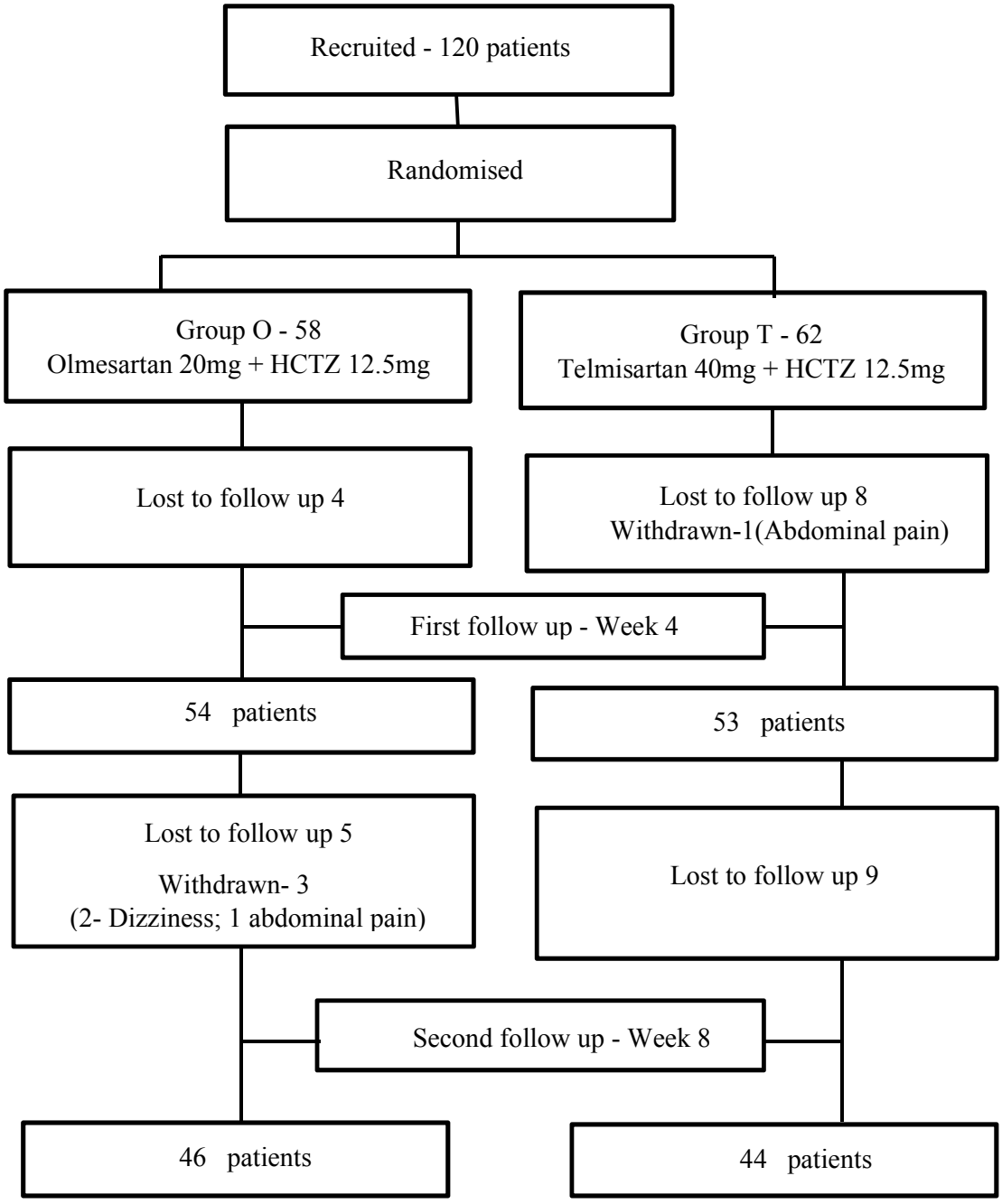

Figure 5. Representing recruitment, randomisation, lost to follow up and those completing the study

Table 6. Demographic data at baseline

Sl no		Group O (Olmesartan+ HCTZ)	Group T (Telmisartan+ HCTZ)	p value
1	Number of patients	46	44	-
2	Mean age (years)	53.6 ± 8.8	53.1 ± 8.5	0.770
3	Gender (M/F)	26/20	25/19	0.573
4	Patients with Type II diabetes mellitus (%)	15 (34.0)	18 (39.1)	0.666
5	Clinical symptoms of hypertension present (%)	15 (32.6)	19 (43.1)	0.385
6	Systolic BP (mmHg)	148.6 ± 5.9	147.9 ± 5.2	0.583
7	Diastolic BP (mmHg)	89.2 ± 5.9	88.1±4.2	0.329
8	Baseline HR (beats/min)	78.0 ± 7.4	77.4 ± 5.5	0.672

Values : Mean ± SD

Majority of patients in both groups were males (56%) and there was family history of hypertension in 11 and 13 patients in groups A and B respectively.

Table 7. Laboratory investigations at baseline

Sl no	Investigations	Group O (n=46)	Group T (n=44)	p value
1	Hb % (g/dl)	13.7 ± 3.8	13.1 ± 3.5	0.674
2	Serum Creatinine (mg/dl)	0.9 ± 0.2	1.0 ± 0.3	0.510
3	Blood Urea (mg/dl)	30.3 ± 8.7	30.1 ± 7.9	0.925
4	Fasting blood sugar (mg/dl)	121.5±31.6	110.9±24.3	0.080
5	Post prandial blood sugar (mg/dl)	186.6±45.5	191.4±51.4	0.630
6	Total cholesterol (mg/dl)	181.2 ± 29.5	180.8 ± 41.3	0.960
7	LDL - cholesterol (mg/dl)	156.4 ± 34.2	151.7 ± 19.4	0.763
8	Triglycerides (mg/dl)	158.4 ± 24.3	157.8 ± 19.1	0.554
9	HDL - cholesterol (mg/dl)	44.1 ± 7.6	43.4 ± 7.5	0.882
10	Serum Sodium (mEq/L)	138.6 ± 2.1	138.1 ± 4.2	0.463
11	Serum Potassium (mEq/L)	4.1 ± 0.4	4.0 ± 0.3	0.316

Values : Mean ± SD

Demographic characteristics and laboratory investigations were comparable between the groups at baseline including liver function tests.

Table 8. Presenting symptoms at baseline

Symptoms	Group O (n=46)	Group T (n=44)
Headache	10 (21.7)	13 (29.5)
Dizziness	5 (10.8)	4 (9.0)
Palpitations	0	2 (4.5)
Epistaxis	1 (2.1)	0

Values in parenthesis represent the percentage

Headache and dizziness were the most common presenting symptoms. Most patients in Group O and Group T (65.2 and 56.8%) were asymptomatic. There was no significant change in the heart rate between baseline and end of the study within and between the two groups.

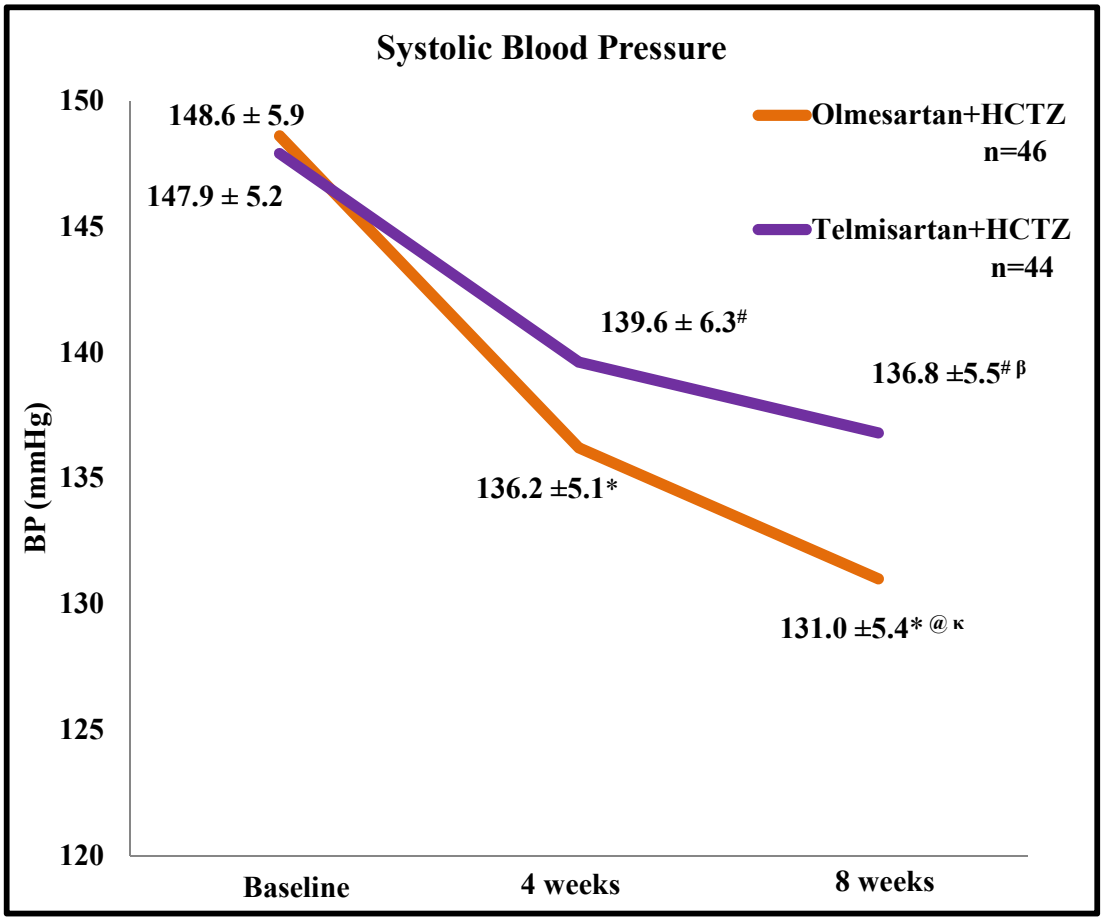

Figure 6. Comparison of systolic blood pressure within and between the groups

*p = 0.0001 Baseline Vs 4th and 8th week
@p = 0.0001 4th week Vs 8th week
} Olmesartan +HCTZ

#p = 0.0001 Baseline Vs 4th and 8th week
βp = 0.002 4th week Vs 8th week
} Telmisartan + HCTZ

$p = 0.006 at week 4
κp = 0.0001 at week 8
} Intergroup comparison

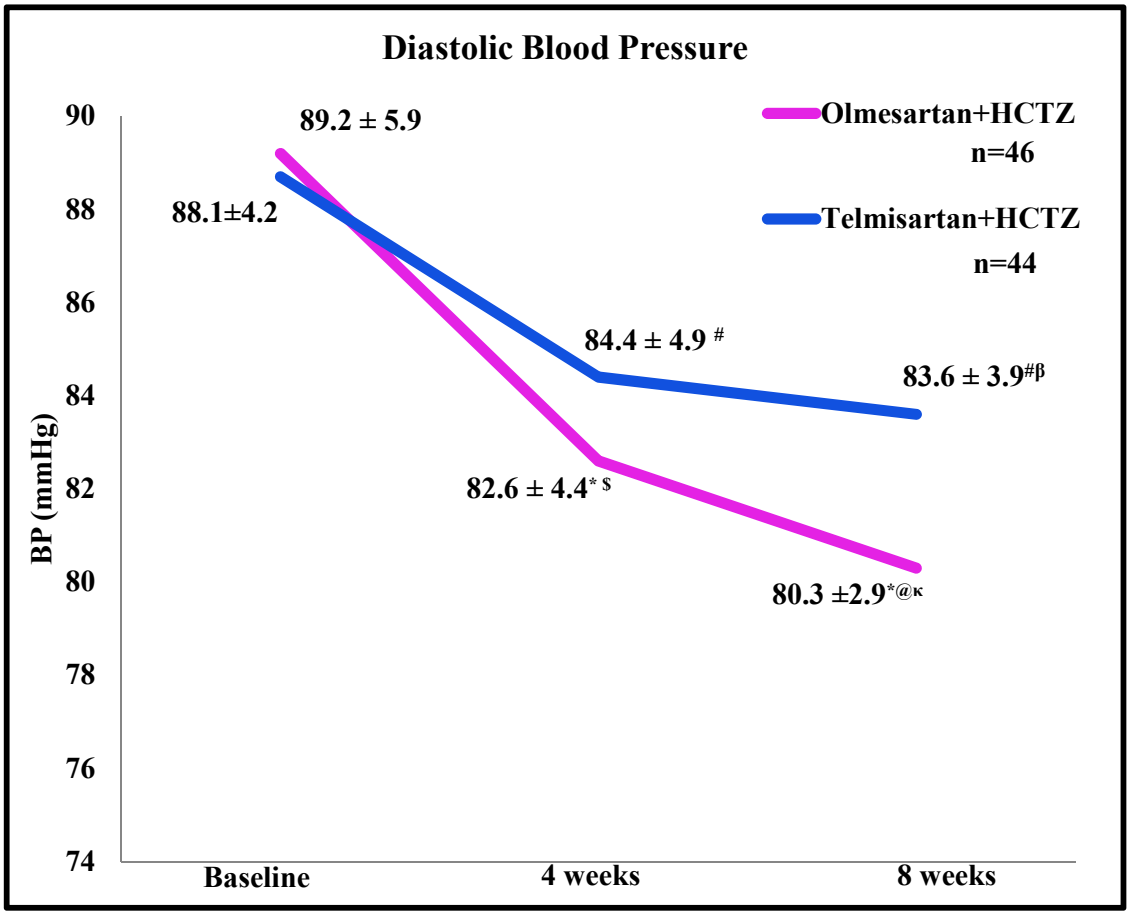

Figure 7. Comparison of diastolic blood pressure within and between the groups

*p = 0.0001 Baseline Vs 4th and 8th week
@p = 0.003 4th week Vs 8th week
} Olmesartan +HCTZ

#p = 0.0001 Baseline Vs 4th and 8th week
βp = 1.000 4th week Vs 8th week
} Telmisartan + HCTZ

$p = 0.19 at week 4
κp = 0.04 at week 8
} Intergroup comparison

In comparison to the baseline there was significant fall in both systolic and diastolic blood pressure at the end of four and eight weeks in the treatment groups.

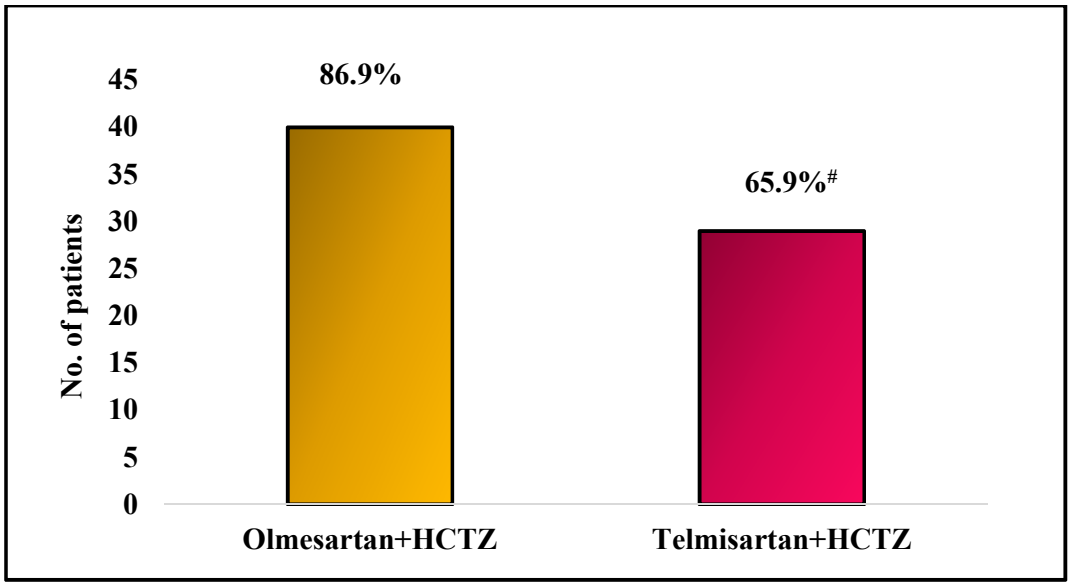

Figure 8. Number of patients with >10mmHg decrease in SBP from baseline to week 8 between the groups

#p = 0.017

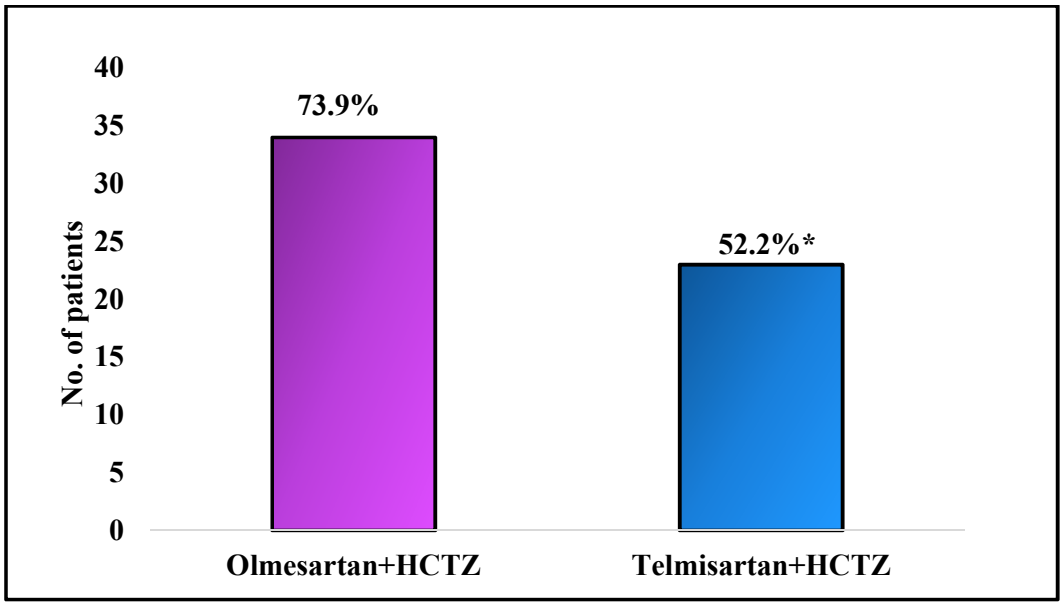

Figure 9. Number of patients with >5mmHg decrease in DBP from baseline to week 8 between the groups

*p = 0.028

Eight weeks after therapy with olmesartan+HCTZ and telmisartan+HCTZ, number of patients who had a decrease of more than 10mmHg in systolic (40 Vs 29) and 5mmHg in diastolic blood pressure (34 Vs 23) compared to baseline with respective drugs is depicted in figures 8 and 9.

There was a significant decrease in both FBS and PPBS at week 8 in those receiving olmesartan+HCTZ, however only PPBS reduced with telmisartan+HCTZ (Table 9). There was no statistical significance when these parameters were compared between the groups (FBS: p=0.069; PPBS: p= 0.674)

Table 9. Blood sugar values at baseline and week 8

	Group O (n=46)			Group T (n=44)		
	Baseline	8 Weeks	p value	Baseline	8 Weeks	p value
FBS (mg/dl)	121.5±31.6	111.5±16.0*	0.006	110.9±24.3	110.0±27.2	0.772
PPBS (mg/dl)	186.6±45.5	168.3±25.3*	0.008	191.4±51.4	170.7±27.6#	0.001

Compared with baseline *p ; # p

In hypertensives with diabetes receiving treatment with study medications (Table 6) both FBS and PPBS decreased significantly at week 8 compared to baseline (Figure 10 , 11). The decrease was greater in those receiving olmesartan+HCTZ, however inter group comparison was not significant.

(FBS: p = 0.056; PPBS: p = 0.224)

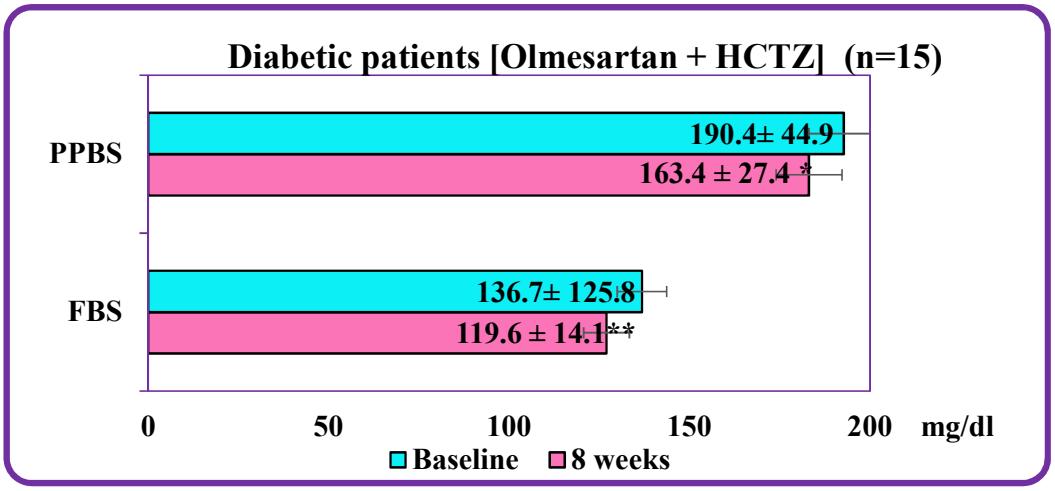

Figure 10. Blood sugar values at baseline and week 8

Baseline Vs Week 8 * p = 0.048 ; ** p = 0.011

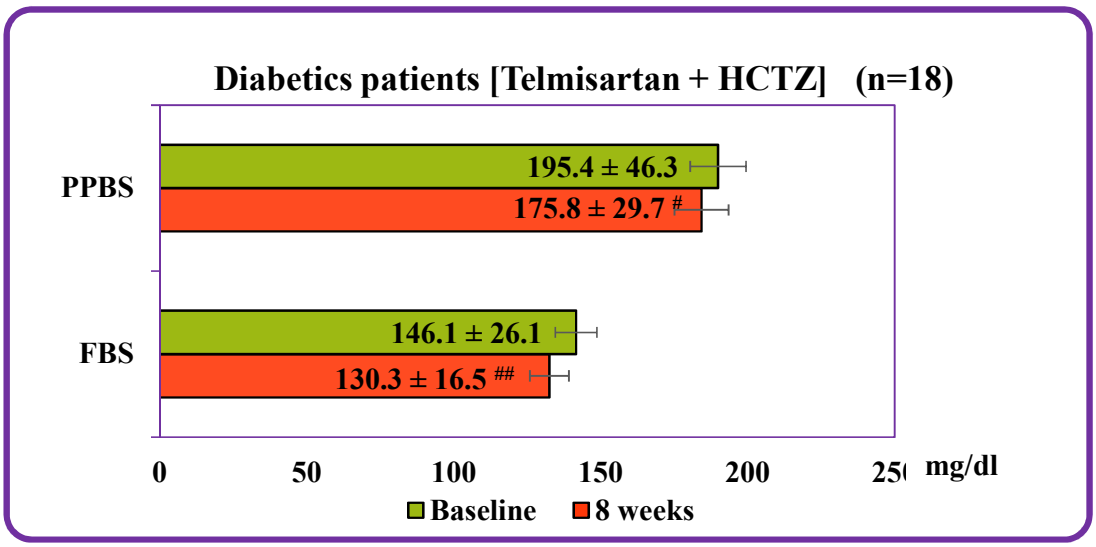

Figure 11. Blood sugar values at baseline and week 8

Baseline Vs Week 8 # p = 0.047 ; ## p = 0.021

Table 10. Comparison of lipid profile and serum electrolytes between baseline and eight weeks

Investigation	Group O (n=46)			Group T (n=44)		
	Baseline	8 Weeks	p value	Baseline	8 Weeks	p value
Total cholesterol (mg/dl)	181.2 ± 29.5	171.6 ± 20.3	0.364	180.8 ± 41.3	172.2 ± 33.8	0.177
LDL - cholesterol (mg/dl)	156.4 ± 34.2	145.6 ± 23.5	0.591	151.7 ± 19.4	149.7 ± 23.9	0.281
Triglycerides (mg/dl)	158.4 ± 24.3	152.5 ± 24.7	0.125	147.8 ± 19.1	144.9 ± 19.7	0.185
HDL - cholesterol (mg/dl)	44.1 ± 7.6	44.3 ± 5.7	0.133	43.4 ± 7.5	44.5 ± 7.6	0.457
Serum Sodium (mEq/L)	138.3 ± 8.9	138.2 ± 5.4	0.183	138.1 ± 4.2	137.6 ± 4.4	0.599
Serum Potassium (mEq/L)	4.1 ± 0.4	4.2 ± 0.3	0.151	4.0 ± 0.3	4.2 ± 0.2	0.729

There was no significant difference between baseline and end of the study within and between the two groups in the above mentioned parameters.

The adverse effects observed were dizziness, abdominal pain and pedal edema as depicted in table 11. These were mild to moderate in intensity and in most patients subsided with time.

Table 11. Adverse effects in patients

Groups	Adverse effect	WHO causality assessment scale	
		Possible	Unlikely
Group O (n=46)	Dizziness- 8	5	3
	Diarrhea- 5	2	3
	Pedal edema- 4	3	1
	Abdominal pain-3	-	3
	Rashes-2	-	2
Group T (n=44)	Dizziness-4	2	2
	Abdominal pain -3	2	1
	Rashes-2	1	1
	Diarrhea-1	-	1

Discussion

Discussion

In India, cardiovascular diseases account for 1.5 million deaths yearly and by 2020, it is predicted to be the leading cause of morbidity and mortality.[46,47] Hypertension is a major risk factor for the development of cardiovascular disease. Rise in systolic and diastolic blood pressure increases the risk of stroke, coronary artery disease, myocardial infarction, cardiac failure and renal disease. Prevalence rates of hypertension in India are 29-45% and 25-38% in men and women respectively. [48,49]

Essential hypertension is associated with an increased activity of the RAAS. Angiotensin II is found to play a central role in vasoconstriction, cell growth, sodium and water retention, and sympathetic activation. It also causes endothelial dysfunction, inflammation, oxidative stress, insulin resistance, and reduced β-cell responsiveness.[50] ARBs block the activity of angiotensin II and reduce proteinuria, improve renal function and attenuate the fibrotic component of left ventricular hypertrophy, therefore they not only control hypertension, but they also prevent cardio renal diseases.[51] These drugs are especially useful in patients having co-morbid conditions such as diabetes mellitus and chronic kidney disease. Monotherapy with ARBs is found to control BP in only 60% of patients with mild to moderate hypertension.[52] Studies show that the efficacy and safety of using any combination therapy is superior to the use of a single drug. Guidelines, therefore recommend initiation of combination therapy when DBP values are >10 mmHg or if SBP is >20 mmHg above the target.[50]

In the present study, 120 patients newly diagnosed with hypertension were randomized and received either olmesrtan+HCTZ or telmisartan+HCTZ (Figure 5), 90 patients completed the eight week study period. The demographic characteristics were comparable (Table 6,7). Most patients were in the fifth decade of life (72.3%). An epidemiological study by Parikh et al showed that 65.2% of people between 51 and 60 years of age suffer from hypertension.[9] We observed that more than 56% of patients were asymptomatic, the diagnosis of hypertension in these patients was thus incidental. The time lapse between onset of hypertension and its diagnosis is delayed due to its silent nature and this may lead to complications which are largely avertible by timely intervention.[53,54] In our study the most common complaints amongst symptomatic patients were headache and dizziness (Table 8). Type II diabetes mellitus was seen in 34 to 39% of our patients. According to the Hong Kong Cardiovascular Risk Factor Prevalence Study, 44% of hypertensives had impaired glucose tolerance.[12] Studies show that there is a significant overlap in the etio-pathogenesis of these two diseases, evidenced by the influence of sympathetic nervous system, RAAS, oxidative stress and adipokines that bring about inflammation and worsen atherosclerosis.[55-60]

We observed that after initiation of therapy with the study medications, patients with initial complaints had symptomatic relief. There was significant reduction in SBP and DBP compared to baseline at 4^{th} and 8^{th} week in both groups. Intergroup comparison at the 4^{th} week showed that there was a statistically significant difference in SBP but not in DBP, whereas at the 8^{th} week this significant difference was observed with both blood pressures (Figure 6 , 7).

Although elevation in both SBP and DBP contribute to worsening of the cardiovascular risk profile, some studies claim that control of systolic hypertension is more important in minimizing morbidity and mortality.[61-64] It has also been proven that a 5–6 mmHg reduction in diastolic BP reduces the risk of stroke and coronary artery disease by 38% and 16% respectively.[65] In this context it can be established that the relationship between elevation in BP and adverse cardiovascular outcome is linear and every mm of Hg reduction offers better prognosis. In the present study, majority of patients in both groups experienced >10mmHg reduction in systolic and >5mmHg reduction in diastolic blood pressure (Figure 8, 9). Intergroup comparison revealed that this number was significant in those receiving olmesartan+ HCTZ. Thus this combination is more efficacious than telmisartan+ HCTZ in lowering blood pressure.

A study on 20 hypertensive patients with early type II diabetes compared the effects of 40mg telmisartan and 20 mg olmesartan monotherapy.[66] The results of this study revealed that in terms of lowering of BP olmesartan was superior to telmisartan. This has been a consistent observation in several other studies involving use of ARBs as monotherapy.[67-71] Relatively few comparative studies have been done on combinations of ARBs and HCTZ. A clinical trial evaluated the effects of olmesartan 20 mg/HCTZ 12.5 mg with losartan 50 mg/ HCTZ 12.5 mg over a period of 12 weeks, it showed that DBP and SBP decreased to a greater extent in the first group.[72] However, one study observed that valsartan/HCTZ produced a higher BP reduction than olmesartan/HCTZ.[73]

It has been shown that both olmesartan and telmisartan improve glycemic control by increasing insulin sensitivity, hence we studied their effect on FBS and PPBS. In the present study, FBS decreased significantly by week eight in patients receiving olmesartan+ HCTZ, but PPBS levels decreased with both drugs (Table 9). Sub group analysis of diabetic patients in our study, showed a reduction in FBS and PPBS in both groups at the second follow up visit, compared to baseline (Figure10 , 11). Intergroup comparison of these parameters in all patients who completed the study and also subgroup analysis of diabetic patients between the two drugs was not significant. Recent data showed that ARBs act as a partial agonist at the PPAR γ – receptor which is found to play a role in increasing insulin sensitivity. [74,75] A study comparing telmisartan 80 mg and losartan 50 mg in hypertensive patients with metabolic syndrome, revealed that only telmisartan improved blood glucose levels.[75] However the findings by Nakayama et al on intergroup comparison of olmesartan(20mg/day) and telmisartan(40mg/day) over three months, did not show any statistically significant difference in the metabolic parameters.[62]

We did not observe a substantial change in the lipid profile of patients in both treatment groups (Table 10). It is likely that a higher dose or longer duration of therapy may be required to observe such effects. The number of adverse effects was slightly higher in patients receiving olmesartan+ HCTZ (Table 11). Dizziness, pedal edema and gastrointestinal intolerance was most common and as per WHO causality assessment scale, the reaction was 'possible' in majority of patients. These events were mild to moderate and subsided on continuation of therapy. As per the results of Daiichi-Sankyo- Integrated Summary of Safety, headache, dizziness and vertigo

occurred most frequently with both drugs, and only 6% of events are reported as severe.[77] Our findings are consistent with existing literature and both treatment groups are found to be well tolerated by patients and hence have a similar safety profile. Three patients receiving olmesartan+ HCTZ and one patient telmisartan+ HCTZ had adverse effects and subsequently dropped out of the study.

Conclusion

Conclusion

- Hypertension is a common non-communicable disease associated with impaired- kidney sodium excretion, increased plasma volume, cardiac output and vascular tone.
- JNC VIII guidelines recommend the use of angiotensin-converting-enzyme inhibitors, angiotensin - receptor blockers, thiazide diuretics or calcium-channel blockers as initial drugs for the treatment of hypertension.
- It has been proven that a 5–6 mmHg reduction in diastolic BP reduces the risk of stroke and coronary artery disease by 38% and 16% respectively. In this context it can be established that the relationship between elevation in BP and adverse cardiovascular outcome is linear and every mm of Hg reduction offers better prognosis.
- In the present study, patients with mild to moderate hypertension were recruited and randomised to receive either olmesartan + hydrochlorothiazide (20+12.5mg) or telmisartan + hydrochlorothiazide (40+12.5mg) orally once daily for eight weeks. They were followed up at the 4^{th} and 8^{th} week.
- At baseline the demographic characteristics and laboratory investigations were comparable between the groups.
- At 4^{th} and 8^{th} week, there was a significant reduction in systolic and diastolic blood pressure compared to baseline in both the groups.
- Intergroup analysis showed that at the 8^{th} week, olmesartan + hydrochlorothiazide reduced both systolic and diastolic blood pressure significantly compared to telmisartan + hydrochlorothiazide

- Subgroup analysis of only the diabetic patients revealed that FBS and PPBS decreased significantly compared to baseline at the end of 8th week in both treatment groups. Comparison between the groups was insignificant.
- No significant change was observed in heart rate, lipid profile and serum electrolytes in both groups.
- Adverse effects reported were similar with both drug combinations; dizziness, pedal edema and gastrointestinal intolerance were common.
- Patients receiving olmesartan + hydrochlorothiazide had greater reduction in systolic and diastolic blood pressure therefore this combination is more efficacious than telmisartan + hydrochlorothiazide in the control of hypertension.

Summary

Summary

Hypertension is the most common cause of cardiovascular disease and is associated with complications like stroke, myocardial infarction and impaired kidney function. In this study 120 patients with mild to moderate hypertension were randomized to receive either olmesartan + hydrochlorothiazide (20+12.5mg) or telmisartan + hydrochlorothiazide (40+12.5mg) orally once daily for eight weeks. Blood pressure and heart rate were recorded at baseline, 4th and 8th week. Laboratory investigations like fasting blood glucose (FBS), post prandial blood glucose (PPBS), lipid profile and serum electrolytes were evaluated at baseline and repeated at the end of 8th week. Adverse effects were also noted.

Ninety patients completed the 8 week study period, 51 were males and 39 females. The mean age was 53.6 ± 8.8 and 53.1 ± 8.5 years in olmesartan + hydrochlorothiazide and telmisartan + hydrochlorothiazide groups respectively and type II diabetes mellitus was present in 34 to 39% of our patients. At baseline the demographic characteristic were comparable between the two treatment groups.

Patients receiving either olmesartan + hydrochlorothiazide or telmisartan + hydrochlorothiazide showed a significant reduction (p=0.0001) in both systolic and diastolic blood pressure at 4th and 8th week compared to baseline. Intergroup comparison of these patients, at the 4th week showed that there was a statistically significant difference in systolic blood pressure (p=0.006) but not in diastolic blood pressure (p=0.19), whereas at the 8th week this significant difference was observed with both systolic (p=0.0001) and diastolic (p=0.04) blood pressures. Sub group analysis of diabetic patients in our study, showed a reduction in FBS and PPBS in both groups at the 8th week, compared to baseline. Intergroup comparison of these parameters in all patients who completed the study and also subgroup analysis of

diabetic patients between the two drugs was insignificant. No significant change was observed in heart rate, lipid profile and serum electrolytes in both groups.

Dizziness, pedal edema and gastrointestinal intolerance were the most common adverse effects and were graded ‘possible’ in majority of patients, according to the WHO causality assessment scale. Both drug combinations were well tolerated and had a comparable safety profile. Thus in our study we observed that olmesartan + hydrochlorothiazide produced a greater reduction in both systolic and diastolic blood pressure than telmisartan + hydrochlorothidazide and is hence a more efficacious drug in the treatment of hypertension.

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Annexures

Proforma

1.Name : 7.Hosp No:

2.Age: 8.Date:

3.Sex:

4.Occupation:

5.Socio economic status:

6.Address:

9.**H/O presenting illness:**

H/O headache : Yes/No

H/O giddiness: Yes/No

H/O epistaxis: Yes/No

H/O angina: Yes/No

H/O stroke: Yes/No

H/O claudication pain Yes/No

10. **Past history**

H/O diabetes mellitus: Yes/No

11. **Family History**

H/O hypertension

H/O diabetes mellitus

12. **Habits**

Diet Vegetarian/ Non Vegetarian

H/O more salt intake Yes/No

H/O alcohol consumption Yes/No

H/O smoking Yes/No

13. **General examination**

Pallor: Lymphadenopathy:

Icterus: Oedema:

Cyanosis: Evidence of Xanthoma:

Clubbing: Arcus senilis in the eye:

	Baseline	4 weeks	8 weeks
BP (mm Hg)			
Heart rate			
Respiratory rate			
Peripheral pulses			

14. **Systemic examination**:

Cardiovascular system : S_1, S_2-

Apical impulse-

Murmurs-

Respiratory system : Type of breath sounds-

Adventitious sounds-

Abdominal examination : Liver-

Spleen-

Renal mass-

Arterial bruits-

Central nervous system : Higher mental functions-

Cranial nerves-

Sensory system-

Motor system-

DTR-

15. **Investigations**:

Complete blood count :

RBC :

WBC:

Platelets:

Hb%:

Renal function tests : Serum creatinine-

Blood urea-

Liver function tests: Total Bilirubin

Alkaline phosphatase

SGOT

SGPT

Blood sugar

	Baseline	8 weeks
Fasting blood sugar (mg/dl)		
Post prandial blood sugar (mg/dl)		

Lipid profile

	Baseline	8 weeks
HDL (mg/dl)		
LDL (mg/dl)		
Total cholesterol (mg/dl)		
Triglycerides (mg/dl)		

Serum electrolytes

	Baseline	8 weeks
Sodium (mEq/L)		
Potassium (mEq/L)		