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Comparative studies of different combination of antihypertensive drugs in the treatment of arterial hypertension

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The objective of the study was to determine the most effective combination of antihypertensive drugs for the treatment of hypertension. The methodology involved conducting a clinical study on 50 patients, administering four different combinations of hypertensive medications and monitoring their clinical and biochemical parameters such as blood pressure, lipid profiles, and blood glucose levels. The results showed that all four classes of anti-hypertensive drugs effectively controlled systolic and diastolic blood pressure, with the triple therapy (C-III) being the most effective. Additionally, the lipid profile of the patients, including total cholesterol, triglycerides, HDL, and LDL levels, was also significantly reduced, which supports the idea that controlling blood pressure has a direct effect on controlling cholesterol levels in the blood of hypertensive patients. The fasting blood glucose level and HbA1c values did not show a direct effect of the anti-hypertensive drugs on glycemic level. The study concluded that the combinational or triple therapy is the most effective way of reducing blood pressure and controlling diabetic complications in hypertensive patients with diabetes. The results also suggest that controlling blood pressure has a direct effect on controlling cholesterol levels in the blood of hypertensive patients.

Keywords: Hypertension, cardiovascular disorders, anti-hypertensive drugs, combination drug therapy, systolic/ diastolic blood pressure, stroke

INTRODUCTION

Hypertension, or high blood pressure, is a medical condition in which there is a persistently increasing force of blood pumped through the heart and blood vessels (Syvolap and Lashkul, 2019). Blood pressure is measured as systolic and diastolic pressure(Flint et al. 2019, McEvoy et al. 2020), with a normal reading being less than 120/80 mmHg(Cheng et al. 2019). According to recent guidelines(Dale et al. 2019), hypertension is defined as systolic pressure of 140 mmHg or higher and diastolic pressure of 90 mmHg(Alam, 2018)or higher, affecting nearly half of the adult population(Flint et al. 2019, Dale et al. 2019).

Hypertension is caused by a combination of factors(Ding and Zhang, 2019)and can be short or long-term. If left untreated for a long period, it can lead to other health complications(Weatherald et al. 2017) such as atherosclerosis, heart failure, chronic kidney disease, dementia, and end-organ damage to the heart, brain, eyes(Cheung et al. 2022), and vasculature(Dale et al. 2019, Kućmierz et al. 2021). It is also a major risk factor for stroke, which is one of the leading causes of death and disability worldwide(Alloubani et al. 2018, Wajngarten and Silva, 2019).

Hypertension is categorized into two types: primary and secondary(Dodson et al. 2018). Primary hypertension is persistently high blood pressure without an underlying condition, while secondary hypertension is caused by another pathological condition(Bădilă et al. 2021). The path physiology of hypertension involves factors such as endothelial damage, the role of aldosterone, oxidative stress, high sodium intake, alcohol consumption, and

irregular sleep patterns(Burns et al. 2019, Bauersachs and López-Andrés, 2022). The RAAS system also plays a significant role in hypertension, as well as risk factors such as age, race, genetic disorders, and lifestyle factors such as physical inactivity and alcohol and tobacco use(Farah et al. 2018).

Treatment for hypertension typically begins with diuretics(Iwakiri and Groszmann, 2020), but combination therapy with various antihypertensive drugs is often recommended(Ssentongo et al. 2020). This is because combination therapy addresses multiple stages of the hypertension mechanism, leading to a more effective recovery for patients(Gausman et al. 2020, Reckelhoff, 2018).Angiotensin converting enzyme inhibitors (ACEIs)(Shukuri et al. 2019), calcium channel blockers (CCBs), angiotensin-receptor blockers (ARBs), beta-blockers, and diuretics are alternative drugs for hypertension therapy(Ogunniyi et al. 2021).

The current project focuses on administering four different combinations of antihypertensive drugs and monitoring their effects on patients by measuring blood pressure, lipid profile, and blood glucose levels over time.

MATERIALS AND METHODS

2.1. Study design and settings:

A clinical study was performed on patients visiting the District Head Quarter Teaching Hospital Dera Ismail Khan and Mufti Mehmood Teaching Hospital Dera Ismail Khan. The data was collected from patients visiting the Cardiology ward, ICU, Medical wards, and local clinical setups of different well-known clinicians at their clinics. A total of 50 patients were selected based on specific inclusion criteria

Characteristics	Description
Age	Patients above 30 years
Sex	Both male and female
Hypertension type	Patients with Atrial hypertension
History of hypertension	Patients taking antihypertensive drugs from at least 5-years
Medication history	Patients taking different combination of antihypertensive drugs
Inheritance	Genetically inherited patients were included
Race	Different races of patients were included

2.2. Materials and equipment:

The following materials and equipment were used in the study: sphygmomanometer, stethoscope, pricking needle, cotton swab, methylated spirit, disposable syringes, blood collection tubes (EDTA, gel tubes), micropipettes, glass slides, chemistry analyzer, hematology apparatus, haemometer, Sahli's haemoglobinometer, buffer, distilled water, pH meter, glucometer, centrifuge, I-Chroma apparatus, and HbA1c cartridge (chroma kit).

2.3. Antihypertensive drug combinations:

Four combinations of antihypertensive drugs were used, including:

- Combination-I: Calcium Channel Blocker (Amlodipine) + Angiotensin Receptor Blocker (Valsartan)
- Combination-II: Angiotensin Receptor Blocker (Valsartan) + Diuretic (Hydrochlorothiazide)
- Combination-III: Calcium Channel Blocker (Amlodipine) + Angiotensin Receptor Blocker (Valsartan) + Diuretic (Hydrochlorothiazide)
- Combination-IV: Diuretic (Hydrochlorothiazide) + Angiotensin Converting Enzymes Inhibitor (Lisinopril)

2.4. Non-invasive blood pressure examination:

The non-invasive arterial pressure was evaluated using a sphygmomanometer and digital apparatus. The systolic and diastolic arterial pressures and heart rhythm were measured against different combinations of anti-hypertensive medicines in the patients. The standard protocol defined by Stergiou et al. was followed for cuff placement and stethoscope examination. The auscultatory technique, also known as the Korotkoff procedure, was used for measuring blood pressure.

Cuff Placement and Stethoscope Procedure

The standard protocol described by Stergiou et al. was followed, which involves measuring the systolic and diastolic arterial pressures of the patients through the use of cuff placement and a stethoscope(Spence and Rayner, 2018).

Auscultatory Technique

Another commonly used method for measuring blood pressure is the auscultatory technique or Korotkoff procedure(Metsios and Kitas, 2018).

2.5. Hemoglobin level monitoring:

The hemoglobin (Hb) level was directly associated with arterial blood pressure and was calculated using a standard automatic analyzer. The glycosylated HbA1C was determined using a Chroma apparatus to estimate the quantity of glycosylated hemoglobin, which is an important parameter in various pathologies such as hypertension and hyperglycemia in diabetes mellitus(Maiti, 2019).

2.6. Glucose level monitoring:

The fasting and random levels of glucose were measured using a digital glucometer with a standard procedure. Monitoring the glucose level is important in hypertensive patients with diabetes because high blood glucose levels can lead to hypertension(Mukhopadhyay et al. 2019).

2.7. Lipid profile monitoring:

The lipid content in the blood of hypertensive patients was regularly monitored as it increases blood thickness

and fat deposition in blood vessels, leading to increased blood pressure and decreased blood flow. The important parameters, including blood cholesterol, low density, and high-density lipoproteins, were measured using a chemistry analyzer(Lee et al. 2015).

RESULTS AND DISCUSSION

3.1. Effect of Combination Therapies on Systolic and Diastolic Blood Pressure:

Fifty patients were examined and the results showed that all four combination therapies significantly reduced both systolic and diastolic blood pressure. Combination-I therapy reduced diastolic blood pressure from 110 to 80 mmHg and systolic blood pressure from 170 to 110 mmHg. Combination-II therapy reduced diastolic blood pressure from 109 to 80 mmHg and systolic blood pressure from 178 to 120 mmHg. Combination-III therapy reduced diastolic blood pressure from 105 to 80 mmHg and systolic blood pressure from 170 to 120 mmHg, and combination-IV therapy reduced diastolic blood pressure from 104 to 80 mmHg and systolic blood pressure from 172 to 118 mmHg.

These results align with previous studies that showed a combination of amlodipine and valsartan to effectively lower blood pressure in hypertensive patients and have better efficacy compared to monotherapy

Table 3.1: Effect of combinations of antihypertensive drugs on systolic and diastolic pressures

Combinations of Anti hypertensive drugs	Systolic blood pressure before therapy (mm of Hg)	Systolic blood Pressure After therapy	Diastolic blood pressure before therapy (mm of Hg)	Diastolic blood pressure after therapy
C-I	170	110	110	80
C-II	178	120	109	80
C-III	170	120	105	80
C-IV	172	118	104	80

A clinical study conducted by Marinier et al. also showed that a combination of ACE inhibitors and Calcium Channel Blockers was more effective in controlling blood pressure than each class given alone. This supports the better efficacy of combination drug therapy as an initial regimen for blood pressure control(Lee et al. 2015).

3.2. Effect of Combination Therapies on Lipid Profile:

An evaluation of lipid profiles with all four combinations of antihypertensive drugs resulted in significant antihyperlipidemic outcomes in terms of total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). The combination III, including ARBs (Valsartan), CCBs (Amlodipine), and diuretics (Hydrochlorothiazide), showed the best results, reducing TC by 19.3 mg/dl, triglyceride by 13.5 mg/dl, HDL by 3.7 mg/dl, and LDL by 12.9 mg/dl. In contrast, combination I, consisting of calcium channel blockers and angiotensin receptor blockers, showed the lowest ant hyperglycemic potential.

A study by Kenichiro et al. showed that a combination of olmesartan (ARB) and azelnidipine (CCB) significantly reduced plasma cholesterol levels in hypertensive patients. These findings support the current study's conclusion that combination therapies are more effective in reducing plasma lipid profiles compared to single-drug antihypertensive therapy. Another study reported that the combination therapy of diuretics (hydrochlorothiazide) and angiotensin receptor blockers (Losartan) reduced high blood pressure by improving lipid profiles and glucose metabolism(Whalen and Stewart, 2008, Lee et al. 2015).

3.3. Effect of Combination Therapies on HbA1C:

The results showed that all combinations of anti-hypertensive drugs had no significant impact on HbA1C levels. The table below summarizes the HbA1C values before and after treatment with combinations C-I, C-II, C-III, and C-IV, which all showed no significant change in the HbA1C levels of the hypertensive patients. This is due to the fact that these drugs belong to the group of anti-hypertensive, which have no effect on blood glucose levels. To achieve a hypoglycemic effect, additional anti-diabetic drugs must be prescribed in conjunction with the anti-hypertensive drugs. A study conducted by Kitamura et al. observed the changes in blood glucose level and HbA1c over a period of 1 year in hypertensive patients after they received ARB (Angiotensin Receptor Blocker) therapy. The blood glucose level showed a slight reduction during the treatment, but there was no correlation between HbA1c value and hypertension of the patient(Benmira et al. 2016).

3.4. Effect of Combination Therapies on Blood Glucose Level:

The antihypertensive combinations showed no significant impact on either fasting or random blood glucose levels, similar to the HbA1C profiles of the patients. Stewart et al. reported that utilizing angiotensin converting enzyme inhibitors may slow progression to kidney failure and cardiovascular mortality, and these agents are the preferred treatment for managing coexisting diabetes and hypertension(Stergiou et al. 2018).

Table 3.2: Effect of combinations of anti-hypertensive drugs on lipid profile

Combinations of antihypertensive drugs	Total Cholesterol (TC, mg/dl)		Triglycerides (TG, mg/dl)		High density lipoprotein (HDL, mg/dl)		Low density lipoprotein (LDL, mg/dl)	
	Before	After	Before	After	Before	After	Before	After
C-I	20.5	19.6	14.4	13.9	4.6	4.4	13.4	13.0
C-II	21	19.4	14.2	13.5	4.7	4.2	14.2	13.1
C-III	22.7	19.3	14.7	13.5	4.7	3.7	13.8	12.9
C-IV	21.7	19.9	14.5	13.8	4.7	4.1	14.2	13.6

Table 3.3: Effect of Combination of Anti-hypertensive drugs on HbA1C level

Combinations	HbA1C before Therapy	HbA1C after Therapy
C-I	6.26 ± 0.4	5.83 ± 0.44
C-II	6.67 ± 0.3	6.38 ± 0.3
C-III	6.54 ± 0.5	6.24 ± 0.4
C-IV	6.58 ± 0.45	6.28 ± 0.39

Table 3.4: Effect of combination of anti-hypertensive drugs on fasting and random blood glucose level

Combinations	Fasting blood Glucose level		Random Blood Glucose level	
	Before Therapy	After Therapy	Before Therapy	After Therapy
C-1	112.7 ± 8.0	108.1 ± 7.8	177.1 ± 14.0	169 ± 12
C-2	113.4 ± 7.0	115.4 ± 6.8	176.5 ± 10.2	180 ± 9.5
C-3	108.2 ± 7.9	111 ± 7.7	169.5 ± 11.8	173.4 ± 11.5
C-4	109.5 ± 7.4	112.3 ± 7.2	171.1 ± 10.9	175.5 ± 10.7

Angiotensin receptor blockers can prevent progression of diabetic kidney disease and are a first-line alternative for patient's intolerant of angiotensin converting enzyme inhibitors. Thiazide diuretics provide additional antihypertensive effects when combined with either angiotensin converting enzyme inhibitors or angiotensin receptor blockers. Beta blockers and calcium channel blockers also had beneficial impacts in managing hypertension in patients with diabetes and reduced cardiovascular events, making them useful in a multi-drug regimen.

CONCLUSION

In the present study, the effects of four different combinations of anti-hypertensive drugs were evaluated on hypertensive patients, including combination-I (Calcium Channel Blockers and Angiotensin Receptor Blockers), combination-II (Angiotensin Receptor Blockers and Diuretics), combination-III (Calcium Channel Blockers, Angiotensin Receptor Blockers and Diuretics), and combination-IV (Diuretics and Angiotensin Converting Enzymes). The evaluation was performed by analyzing various parameters such as systolic and diastolic blood pressure, lipid profiles, fasting and random blood glucose levels, and glycosylated Hemoglobin (HbA1c) levels. The results showed that all four combinations of anti-hypertensive drugs effectively controlled systolic and diastolic blood pressure in hypertensive patients, with combination III (Amlodipine, valsartan and hydrochlorothiazide) demonstrating the most significant control over the contributing parameters.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors contributed equally. All authors read and approved the final version.

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