ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 10, Issue 2, 2017

Online - 2455-3891
Print - 0974-2441

Research Article

COMPARISON OF EFFICACY AND ADVERSE DRUG REACTIONS OF MONOTHERAPY VERSUS COMBINATION THERAPY OF ANTIHYPERTENSIVES AMONG DIABETIC HYPERTENSIVE PATIENTS IN A TERTIARY CARE HOSPITAL

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Received: 24 October 2016, Revised and Accepted: 03 November 2016

ABSTRACT

Objective: To compare the efficacy and adverse drug reactions of monotherapy and combination therapy of antihypertensive drugs in diabetic hypertensive patients.

Methods: A prospective observational study of 18 months duration was conducted in the Department of Medicine of a tertiary care hospital in South India. A total of 200 patients were included in the study. Using a standard proforma, the details of patients such as demographic data and antihypertensive medications were collected and analyzed for efficacy and safety.

Results: Of 200 patients studied, 50% received monotherapy whereas the remaining 50% received combination therapy. There was male preponderance (54%) in the study population, with the mean age being 60.07±11.32 years. In monotherapy group, most commonly prescribed drug was amlodipine (38%), whereas in combination group, angiotensin receptor blocker (ARB) or calcium channel blocker (CCB) + beta blocker (18%) was commonly prescribed among 2-drug group and ARB+ thiazide+ CCB (25.6%) among 3-drug group. Monotherapy and combination therapy were analyzed to be equally efficacious in reducing systolic blood pressure and diastolic blood pressure. Based on the adverse effect profile, monotherapy comparatively produced more adverse effects than combination group. Amlodipine-induced pedal edema (56.7%) was the most common adverse effect observed, and it was predominantly managed by changing it to be a better tolerable CCB, namely cilnidipine.

Conclusion: The combination therapy may be a better treatment option in selected patient population.

Keywords: Systolic blood pressure, Diastolic blood pressure, Amlodipine, Cilnidipine, Pedal edema.

 DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10i2.15854

INTRODUCTION

Hypertension (HTN) is one of the most common chronic diseases and is defined as systolic blood pressure (SBP) ≥140mm Hg and/or diastolic blood pressure (DBP) ≥90mm Hg [1]. It exerts a considerable health burden on the public regarding its significance in cardiovascular health and thereby the well-being in India [2,3]. HTN is unswervingly accountable for 57% of all stroke and 24% of all coronary heart disease (CHD) deaths in India [4] and this correlation is more associated with SBP than with DBP [5]. Globally, it is indeed a vital test in public health due to its high occurrence and related death [6-8].

HTN is a very familiar comorbid state in diabetes wherein approximately 20-60% of patients with diabetes are affected. HTN extensively intensifies the danger of both macrovascular and microvascular complications, including cerebrovascular disease, CHD, and peripheral vascular disease. Based on convincing data, pharmacological therapy of HTN in patients with diabetes is effective in producing considerable decrease in these complications. The presence of a firm epidemiological relation between HTN in diabetes and undesirable consequences of diabetes has been established, but reduced information from trials evaluating different classes of antihypertensive drugs in patients with HTN associated with diabetes still persists [9]. The intricacy of various pathophysiological processes that lead to rise in BP is such that a judicious and systematic mode of antihypertensive treatment is hardly achievable in any hypertensive patient [10]. However, there are a variety of drugs available for the treatment which can be used alone or in combination to reduce arterial pressure accordingly [11].

The present-day recommendations include a universal approach in controlling HTN, with not much importance given on determining a curative modality based on the various underlying pathophysiology of HTN. Considering the fact that there has been an improved understanding of a specific etiology, it has now become feasible to develop therapies selective for distinct pathophysiological mechanisms with fewer adverse effects, resulting in more effective BP reduction [12,13]. Thus, it is considered that with the practice of novel usage of hereditary science unified with an understanding of systemic functioning and population studies, there will be more selective and efficacious methods possible in treating and even averting HTN in the future years [14,15].

Hence, considering the fact that there have been limited data from trials comparing monotherapy and combination therapy of different classes of antihypertensive drugs in patients with diabetes and HTN, the present study was planned to assess the efficacy and adverse effects of monotherapy and combination therapy of antihypertensive drugs among diabetic hypertensive patients.

METHODS

This prospective observational study was conducted in the Department of Medicine of a tertiary care hospital in South India for 18 months (1st November 2013 to 30th April 2015). The Institutional Ethics

Committee (IEC) clearance was obtained before initiation of the study (letter no. IEC 513/2013). A total of 200 diabetic hypertensive patients fitting into the subject selection criteria were included in the study. They were broadly divided into two treatment groups that included monotherapy and combination therapy groups wherein combination was further divided into 2-drug and 3-drug combination groups; hence, Group 1 is monotherapy, Group 2 is 2-drug, and Group 3 is 3-drug combination group. Subject selection criteria were as follows:

Inclusion criteria

1. Patient of either male or female sex and age group of 18-80 years diagnosed with diabetic HTN.
2. Diabetic hypertensive patients with comorbidities such as stroke and myocardial infarction.

Exclusion criteria

1. Patients diagnosed to have chronic kidney diseases (having creatinine values >2 mg/dL), peripheral vascular diseases, and respiratory comorbidities.
2. Patients on steroid medications.
3. Pregnant and lactating mothers.

Patients (outpatients) fulfilling the study criteria were included after obtaining consent and were reviewed for efficacy and adverse drug reaction (ADR) of the prescribed drugs.

1. Demographic and clinical data of each patient (age, sex, and available laboratory reports) were collected.
2. Efficacy of monotherapy and combination therapy of antihypertensive drugs was compared.
   - Baseline value was obtained based on patient's initial visit before treatment.
   - Two follow-up BP values were noted following the initiation of treatment (ideally, at 4th and 8th week after starting treatment).
   - The percentage decrease in SBP and DBP observed over a period of 2 follow-up visits was thereby assessed for efficacy using the following formula.

$$\text{Percentage reduction in BP} = \frac{\text{Baseline BP} - \text{Second follow up visit reading (at end of study)}}{\text{Baseline}} \times 100$$

3. The details of suspected ADRs were documented in a suitably designed Central Drugs Standard Control Organization suspected ADR form. Causality assessment was done using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system [16].

Statistical analysis

Demographic data were analyzed using descriptive statistics. For efficacy parameter, the mean percentage reduction in BP from baseline to the end of the study (at 2nd follow-up visit) was calculated for individual drugs and combinations in all the three groups. Mean SBP and DBP before and after treatment within each group was compared using paired t-test. Mixed design analysis of variance (ANOVA) model was used to compare SBP and DBP between the groups. $p<0.05\%$ was considered statistically significant. ADRs were analyzed using descriptive approach. Data were analyzed using SPSS software version 16.

RESULTS

A total of 200 outpatients having HTN associated with diabetes, based on the subject selection criteria, were enrolled and analyzed for demographic characteristics, drug utilization pattern, efficacy analysis of treatment group, and ADR due to prescribed drugs.

Patients were divided eventually into three groups depending on the treatment they received as shown in Table 1. The mean age of patients in the study population was 60.07±11.32 years. They were divided into different age groups (Fig. 1). The majority of the patients were in the 60-69 years age group (32%) followed by 50-59 years age group (28%). There was a male predominance (54%) in the study population (Fig. 2).

As shown in Table 2, among all the 100 patients receiving monotherapy, most of the patients received amlodipine (38%) followed by enalapril (23%). The least prescribed drug among patients receiving monotherapy was clonidine (4%). In Group 2 containing 61 patients, the most commonly prescribed combinations were beta blocker + calcium channel blocker (CCB) and angiotensin receptor blocker (ARB) + CCB (18%) as shown in Table 3. Moreover, among Group 3 that comprised 39 patients, the most commonly prescribed combination group was ARB + thiazide + CCB (25.6%) as shown in Table 4.

The percentage reduction in SBP among monotherapy group is shown in Table 5. The highest reduction was seen in metoprolol group (16.8%)

Table 1: Group-wise distribution of patients

Drug group	Number of patients (n=200)
Group 1 (monotherapy)	100
Group 2 (2 drug combination)	61
Group 3 (3 drug combination)	39

Table 2: Drug utilization pattern in monotherapy group

Drug name	Number of patients (%)
Amlodipine	38 (38)
Enalapril	23 (23)
Cilnidipine	16 (16)
Metoprolol	09 (9)
Prazosin	05 (5)
Telmisartan	05 (5)
Clonidine	04 (4)

ACE: Angiotensin-converting enzyme, CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker

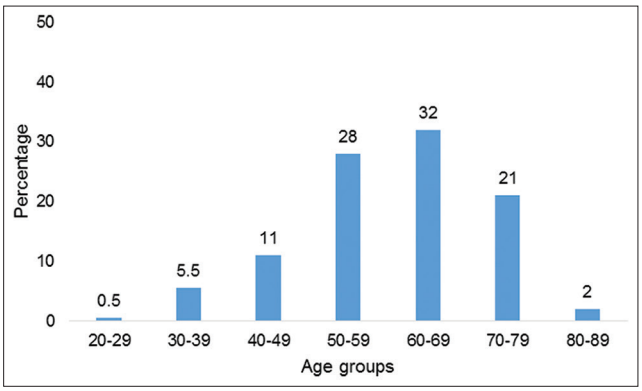

Fig. 1: Age group distribution of patients

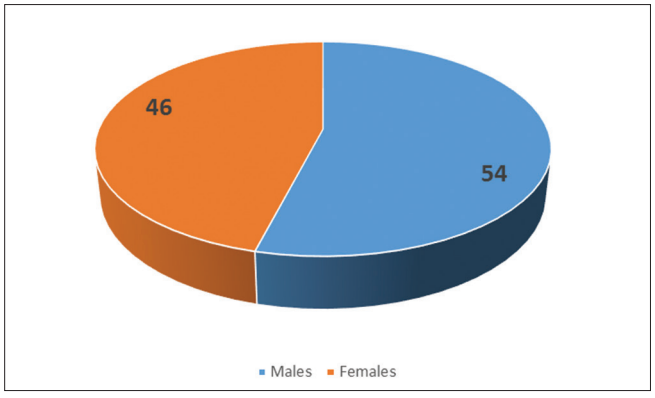

Fig. 2: Gender distribution of patients in percentage

followed by enalapril group and the least reduction was seen in the telmisartan group (12.6%). All the medications in Group 1 brought about a statistically significant reduction in percentage decrease in SBP. As shown in Table 6, patients treated with cilnidipine showed the highest reduction in DBP (15.1%) followed by amlodipine (12.8%). Least reduction in DBP was seen in prazosin group (11.1%) which was not statistically significant. All the other drugs in the monotherapy group showed a statistically significant decrease in DBP. In Group 2, angiotensin-converting enzyme (ACE) inhibitor + CCB combination showed the greatest reduction in SBP (15.6%) followed by alpha agonist + CCB combination (15.3%). Least reduction in SBP was seen in thiazide + CCB combination (11.8%). The percentage reduction in SBP was statistically significant in all the combinations in Group 2 as shown in Table 7. ARB or beta blocker + CCB combination showed the maximum percentage reduction in DBP (12.5%) followed by ACE inhibitor + CCB combination (11.9%). The least reduction was observed in thiazide + CCB group. The reduction was statistically significant with all the drug combinations as shown in Table 8. As shown in Table 9, in Group 3, there was a comparatively higher percentage reduction in SBP seen in the ARB + CCB + alpha agonist group (17.1%), the least being in the ACE inhibitor + CCB + alpha agonist group (9.6%). All the results were statistically significant. As shown in Table 10, ARB + thiazide + CCB (14.4%) combination showed greater percentage decrease in DBP with the least decrease seen in ACE inhibitor + CCB + alpha agonist (11.6%) combination. The reduction was statistically significant with all the combinations. The fall in SBP and DBP, when compared to the three groups, at baseline and 1 and 2 months, was not statistically significant as per the analysis done using mixed design ANOVA (Figs. 3 and 4).

Table 3: Drug utilization pattern in 2-drug combination group

Drugs	Number of patients (%)
ACE inhibitor+CCB	10 (16.4)
Alpha agonist+CCB	10 (16.4)
Beta blocker+CCB	11 (18.0)
ARB+CCB	11 (18.0)
Thiazide+CCB	08 (13.2)
Others*	11 (18.0)

CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, *Others represent ARB+alpha$_2$ agonist, ACE inhibitors+Alpha$_2$ agonist, loop diuretics+CCB etc., ACE: Angiotensin-converting enzyme

Table 4: Drug utilization pattern in 3 drug combination group

Drugs	Number of patients(%)
ARB+thiazide+CCB	10 (25.6)
ACE inhibitor+CCB+alpha agonist	09 (23.1)
ARB+CCB+alpha agonist	09 (23.1)
Others*	11 (28.2)

CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, *Others represent β-blocker+alpha blocker+alpha$_2$ agonist, beta blocker+thiazide+alpha blocker etc., ACE: Angiotensin-converting enzyme

As shown in Tables 11-14, of 200 patients, 30 (15%) patients developed ADRs. Most of the drug reactions were seen in the monotherapy group (66.7% of the total ADRs). Rest of the ADRs were seen among the combination groups (33.3% of total ADRs). Amlodipine-induced pedal edema was the most common ADR among the three groups (56.7%). All ADRs were classified as "possible" according to WHO-UMC causality assessment scale.

DISCUSSION

The present study suggested that most of the patients (32%) having HTN associated with diabetes belong to age group of 60-69 years followed by 28% belonging to the age group of 50-59 years; the mean age of the study population was 60.07±11.32 years. The least percentage of patients (0.5%) was seen in 20-29 years age group. Supporting this, according to Everett *et al.*, the incidence of HTN was more commonly seen in patients below 65 years (85.9-87.7%) in comparison to patients above 65 years (12.3-14.0%) [17]. Lacourciere *et al.* [18] and Ruilope *et al.* levels [19] had also been consistent with the current study showing the mean age to be 60-61 years; however; in a study carried out by Yasmeen *et al.*, 31.7% patients belonged to 51-60 years age group followed by 28.9% in 41-50 years age group with the least (3.5%) being 71-80 years age group [20]. The rationale for an increase in blood pressure with age could probably be due to structural changes in the arteries and especially with large artery stiffness [21].

In the present study, there was male preponderance in patients having HTN with diabetes (54%). Previous studies conducted in India (Yasmeen *et al.*, Jaganan *et al.*), USA (Everett *et al.*), Nepal (Pandaya *et al.*), and Australia (White *et al.*) have also reported that the incidence of HTN with diabetes mellitus was higher in males compared to females [17,20,22-24]. This could probably be due to significantly higher awareness, treatment, and control rates among women than men as supported by a recent data from the 2007 to 2010 National Health and Nutrition Examination Survey [25].

The most common groups of antihypertensive drugs such as CCBs, beta blockers, ACE inhibitors, ARBs, alpha blockers, alpha agonists, and diuretics were used to treat HTN in the present study. Among these, the most frequently used antihypertensive as monotherapy was amlodipine (38%) followed by enalapril (23%). Alavudeen *et al.* showed similar finding wherein the most commonly prescribed drug among monotherapy was CCB (34.3%) followed by ACE inhibitors (29.9%) [26]. This was also seen by Kousalya *et al.*, where amlodipine (83.8%) was the most commonly used drug [27]. Diuretics were not prescribed as a monotherapy in this study, which was different from studies done by Tamuno and Fadare and Etuk *et al.* wherein diuretics were the regularly prescribed drug (41.2% and 44.8%, respectively) as monotherapy [28,29]. However, according to the WHO guidelines, ACE inhibitors are ideally regarded as the favored therapy in patients with HTN and diabetes [30]. Findings from the heart outcomes prevention evaluation study also support the above guidelines [31]. According to Bronsert *et al.*, Kaur *et al.*, Jaganan *et al.*, and Beulah *et al.*, the most commonly prescribed class of drug was ACE inhibitor (43.6%, 33.8%, 52.3%, and 56.7%, respectively) [22,32-34].

Table 5: Effect of monotherapy on systolic blood pressure (n=100)

Drugs	Systolic BP (mm HG)		Mean decrease in SBP (mm HG)	Percentage decrease in SBP	p
	Baseline (mean±SD)	After (mean±SD)			
Amlodipine	162.6±11.0	137.2±13.3	25.4±4.2	15.6	<0.001*
Enalapril	158.7±6.9	132.4±7.3	26.3±7.9	16.6	<0.001*
Cilnidipine	159.6±7.4	133.7±8.8	25.8±5.6	16.2	<0.001*
Metoprolol	160.0±8.6	133.1±12.9	26.8±11.9	16.8	<0.001*
Prazosin	160.0±7.0	138.0±8.3	22.0±4.4	13.7	<0.001*
Telmisartan	162.0±8.3	141.6±2.1	20.4±6.5	12.6	<0.05*
Clonidine	155.0±5.7	132.5±12.5	22.5±9.5	14.5	<0.05*

SD: Standard deviation, SBP: Systolic blood pressure, mm Hg is Millimeter of mercury, SD is standard deviation for n=100 observations. *represents statistical significance

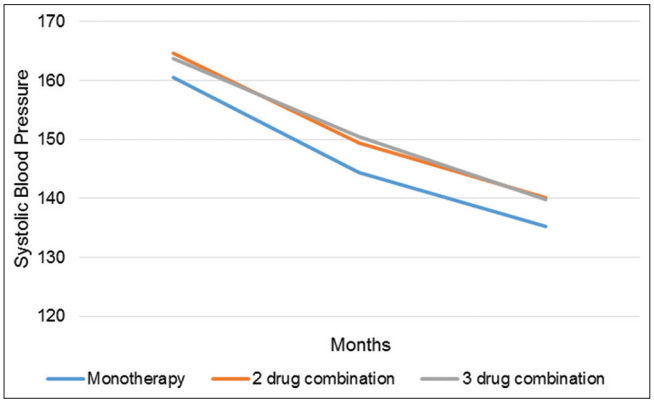

Fig. 3: Comparison of fall in systolic blood pressure between monotherapy and combination group

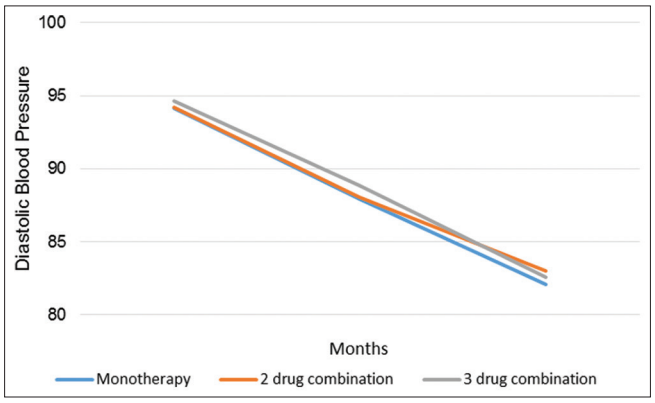

Fig. 4: Comparison of fall in diastolic blood pressure between monotherapy and combination group

Table 6: Effect of monotherapy on diastolic blood pressure (n=100)

Drugs	Diastolic BP (mm HG)		Mean decrease in DBP (mm HG)	Percentage decrease in DBP	p
	Baseline (mean±SD)	After (mean±SD)			
Amlodipine	95.4±9.3	83.2±7.1	12.2±6.2	12.8	<0.001*
Enalapril	95.0±5.8	83.4±6.4	11.5±6.0	12.2	<0.001*
Cilnidipine	92.0±6.5	78.1±6.5	13.8±6.3	15.1	<0.001*
Metoprolol	91.1±7.8	80.0±5.0	11.1±6.0	12.2	<0.05*
Prazosin	90.0±7.0	80.0±7.0	10.0±10.0	11.1	0.089
Telmisartan	96.0±5.4	84.0±5.4	12.0±4.4	12.5	<0.05*
Clonidine	95.0±5.7	84.0±4.8	11.0±2.0	11.6	<0.05*

SD: Standard deviation, DBP: Diastolic blood pressure, mm Hg is Millimeter of mercury, SD is standard deviation for n=100 observations. *represents statistical significance

Table 7: Effect of 2 drug combination on systolic blood pressure (n=61)

Drugs	Systolic BP (mm HG)		Mean decrease in SBP (mm HG)	Percentage decrease in SBP	p
	Baseline (mean±SD)	After (mean±SD)			
ACE inhibitor+CCB	162.4±4.1	137.0±11.5	25.4±9.5	15.6	<0.001*
Alpha agonist+CCB	184.6±13.5	156.2±11.6	28.4±6.9	15.3	<0.001*
Beta blocker+CCB	159.8±6.0	137.0±8.2	22.7±8.0	14.2	<0.001*
ARB+CCB	165.5±12.1	140.3±11.8	25.0±9.6	15.2	<0.001*
Thiazide+CCB	155.0±5.3	136.7±6.4	18.2±8.2	11.8	<0.001*
Others	160.0±7.7	134.0±10.1	26.0±10.7	16.2	<0.001*

SD: Standard deviation, SBP: Systolic blood pressure, CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, mm Hg is Millimeter of mercury, SD is standard deviation for n=61 observations, *represents statistical significance, ACE: Angiotensin-converting enzyme

Table 8: Effect of 2-drug combination on diastolic blood pressure (n=61)

Drugs	Diastolic BP (mm HG)		Mean decrease in DBP (mm HG)	Percentage decrease in DBP	p
	Baseline (mean±SD)	After (mean±SD)			
ACE inhibitor+CCB	92.0±9.1	81.0±7.3	11.0±5.6	11.9	<0.001*
Alpha agonist+CCB	98.4±6.0	88.0±4.2	10.4±3.6	10.5	<0.001*
Beta blocker+CCB	94.5±5.2	82.7±6.4	11.8±6.0	12.5	<0.001*
ARB+CCB	96.7±8.8	84.5±6.8	12.1±6.6	12.5	<0.001*
Thiazide+CCB	91.2±3.5	83.0±4.5	8.2±3.6	9.0	<0.001*
Others	91.8±6.0	79.0±7.0	12.7±7.8	13.8	<0.001*

SD: Standard deviation, CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, mm Hg is Millimeter of mercury, SD is standard deviation for n=100 observations, *represents statistical significance, ACE: Angiotensin-converting enzyme

It was seen in the current study that majority of the patients received beta blocker + CCB (18%) and ARB + CCB (18%) among the 2-drug combination group. This is in agreement with the study conducted by Panda *et al.,* wherein the most common 2-drug combination prescribed was CCB+ beta blocker (30.3%) followed by CCB + ARB (25.9%) [35]. Alavudeen *et al.* also reported that CCB+ARB (25%) was the common drug prescribed among the 2-drug combination group [26]. However, most of the other studies had shown an inconsistent finding with the present study in relation to the most common 2-drug combination drugs prescribed. Tamuno and Fadare and Pandaya *et al.* reported that the most commonly used 2-drug combination was CCB + diuretic (12% and 37.8%, respectively) [23,28]. According to Kausalya *et al.*, ACE inhibitor + CCB was the most commonly prescribed 2-drug combination, whereas in a study by Jaganan *et al.*, ACE inhibitors

Table 9: Effect of 3-drug combination on systolic blood pressure (n=39)

Drugs	Systolic BP (mm HG)		Mean decrease in SBP (mm HG)	Percentage decrease in SBP	p
	Baseline (mean±SD)	After (mean±SD)			
ACE inhibitor+CCB+Alpha agonist	166.6±5.0	150.6±5.0	16.0±3.8	9.6	<0.001*
ARB+thiazide+CCB	162.0±7.8	135.0±9.7	27.0±4.8	16.7	<0.001*
ARB+CCB+Alpha agonist	164.0±6.6	136.0±5.3	28.0±7.2	17.1	<0.001*
Others	162.9±4.5	138.5±6.0	24.3±5.1	14.9	<0.001*

SD: Standard deviation, CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, SBP: Systolic blood pressure, mm Hg is Millimeter of mercury, SD is standard deviation for n=39 observations, *represents statistical significance, ACE: Angiotensin-converting enzyme

Table 10: Effect of 3-drug combination on diastolic blood pressure (n=39)

Drugs	Diastolic BP (mm HG)		Mean decrease in DBP (mm HG)	Percentage decrease in DBP	p
	Baseline (mean±SD)	After (mean±SD)			
ACE inhibitor+CCB+Alpha agonist	95.5±5.2	84.4±5.2	11.1±3.3	11.6	<0.001*
ARB+thiazide+CCB	97.0±6.7	83.0±6.7	14.0±6.9	14.4	<0.001*
ARB+CCB+Alpha agonist	95.5±7.2	82.2±4.4	13.3±5.0	13.9	<0.001*
Others	90.9±5.3	80.9±5.3	10.0±6.3	11.1	<0.001*

SD: Standard deviation, CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, DBP: Diastolic blood pressure, mm Hg is Millimeter of mercury, SD is standard deviation for n=39 observations, *represents statistical significance, ACE: Angiotensin-converting enzyme

Table 11: Group-wise ADR analysis

Drug group	Number of ADRs (n=30)
Monotherapy	20 (66.7)
2-drug combination	06 (20.0)
3-drug combination	04 (13.3)

ADR: Adverse drug reaction

Table 12: Drug-wise adverse drug reaction analysis

Drug name	ADR	n=30
Amlodipine	Pedal edema	17 (56.7)
Enalapril	Dry cough	05 (16.7)
	Acute kidney injury	01 (3.3)
Telmisartan	Dry cough	02 (6.7)
	Hyponatremia	01 (3.3)
	Hyperkalemia	01 (3.3)
Hydrochlorothiazide	Hypokalemia	03 (10.0)

ADR: Adverse drug reaction

Table 13: Adverse drug reactions in monotherapy group

Drug	ADR	Number of ADRs (n=20)
Amlodipine	Pedal edema	13 (65%)
Enalapril	Dry cough	03
	Acute kidney injury	01 (20%)
Telmisartan	Dry cough	01
	Hyponatremia	01
	Hyperkalemia	01 (15%)

ADR: Adverse drug reaction

with thiazide diuretics (34.3%) were the most commonly prescribed combination [22,27].

In the present study, the most commonly prescribed 3-drug combination was ARB+ thiazide+ CCB (25.6%) followed by an equal percentage of 23.1% for ACE inhibitor+ CCB+ alpha agonist and ARB+ CCB+ alpha agonist. Similarly, Alavudeen *et al.* reported that ARB+ CCB+ diuretic (21.4%) was the most commonly used 3-drug combination [26]. Panda *et al.* had also shown ARB+ thiazide+ CCB (1.9%) as the most common 3-drug combination prescribed, hence showing consistency [35]. According to Tamuno and Fadare and Kousalya *et al*., ACE inhibitor + diuretic + CCB (14.5% and 34.4%, respectively) was commonly used in the 3-drug combination group [27,28]. However, according to Etuk *et al.,* inclusion of alpha methyldopa in the 3-drug combination therapy was found to be more common in the form of alpha methyldopa + ACE inhibitor + diuretic combination (17.2%) [29]. This was different from the present study wherein clonidine was the most frequently used alpha agonist used in combination with CCB and ARB or ACE inhibitor (23%).

We found that, among the monotherapy group, metoprolol showed maximum percentage reduction in SBP (16.8%) followed by a reduction of 16.6% seen in the enalapril group. This finding was supported by another study conducted by Beulah s *et al.* wherein beta blockers produced a greater percentage reduction of 31.1% followed by a 28.5% reduction seen in ACE inhibitors [34]. However, in a study conducted by Yasmeen *et al.,* enalapril showed greater percentage reduction in SBP (18.8%) followed by 14.1% reduction in atenolol [20]. In relation to DBP, maximum percentage reduction was seen in the CCB group where the novel calcium antagonist cilnidipine produced 15.1% reduction followed by 12.8% reduction seen in amlodipine. This was supported by Etuk *et al.* where CCB monotherapy had shown to be effective in reduction of DBP (13.4%) [29]. However, in other studies where beta blockers and ACE inhibitors were predominantly used as monotherapy, beta blockers produced comparatively greater percentage decrease in DBP (15.1% and 18.3%, respectively) than ACE inhibitors (14.9% and 15.9%, respectively) [20,34].

Among the 2-drug combination group, we observed greater percentage reduction in SBP (15.6%) with ACE inhibitor + CCB group. This finding was consistent with earlier studies wherein the ACE inhibitor + CCB group showed a greater percentage reduction (21.8%) in comparison to the other 2-drug combination groups [20,36-38]. In our study, we found a greater percentage decrease in DBP with ARB + CCB and beta blocker + CCB group (12.5%). According to Chrysant *et al.*, ARB + CCB combination has shown to be effective [39]. A retrospective cohort study by Bisognano *et al.* showed that beta blocker + CCB group was more effective than beta blocker + ACE inhibitor and beta blocker + ARB combination as it had produced a 9.4% reduction in DBP [40]. However, in other studies such as Yasmeen *et al.* and Beulah *et al.*, CCB + diuretic group had shown a greater reduction in DBP of 17.7% and 18.8%, respectively [20,34].

Table 14: Adverse drug reactions in combination groups

2 Drug combination			
Combination	**Implicated drug**	**Adverse drug reaction**	**Number of ADRs (n=6)**
CCB+Thiazide	Thiazide	Hypokalemia	3 (30)
ARB+Thiazide			
ARB+CCB	Amlodipine	Pedal edema	2 (20)
ACE inhibitor+CCB			
ACE inhibitor+CCB	Enalapril	Dry cough	1 (10)
ARB+Thiazide+CCB	Amlodipine	Pedal edema	2 (20)
3 Drug combination			
Combination	Implicated drug	Adverse drug reaction	Number of ADRs (n=4)
ACE inhibitor+beta blocker+alpha blocker	Enalapril	Dry cough	1 (10)
ARB+thiazide+alpha blocker	Telmisartan	Dry cough	1 (10)

CCB: Calcium channel blocker, ARB: Angiotensin receptor blocker, ADR: Adverse drug reaction, ACE: Angiotensin-converting enzyme

In the present study, among the 3-drug combination group, ARB+ CCB+ alpha agonist had shown a greater percentage decrease in SBP (17.1%) whereas ARB+ thiazide+ CCB (14.4%) showed the best reduction in DBP. Maladkar *et al.* and Oparil *et al.* had shown the superiority of ARB+ thiazide+ CCB triple combination for control of DBP [41,42]. However, in the study by Yasmeen *et al.*, beta blocker+ CCB+ ACE inhibitor produced maximum percentage decrease in SBP and DBP (16.6% and 29.2%, respectively), whereas according to Beulah *et al.*, ACE inhibitor + beta blocker + diuretic led to a greater percentage decrease in both SBP and DBP (39% and 18.3%) [20,34].

Upon comparison of efficacy between monotherapy and combination therapy of antihypertensives, it was seen that both were equally effective. Consistent with above findings, Yasmeen *et al.* had shown that all groups in monotherapy and combination therapy were equally effective in reducing BP [20]. Similarly, Beulah *et al.* also supported the present study with the same findings [34]. However, according to a meta-analysis conducted by Wald *et al.* on 11,000 patients from 42 trials, combination of antihypertensive drugs from various classes is approximately 5 times more efficient than a 2-fold increase in the dose of one drug [43]. This could be due to synergistic action of individual antihypertensive drugs upon combination.

As shown in results, 15% of patients developed ADRs and most of the ADRs were seen in the monotherapy group (66.7%). However, according to Husain *et al.*, combination therapy had shown drastically higher occurrence of ADRs of 61.8% as compared to monotherapy showing 38.2% of drug reactions [44]. This could probably be due to summation or additive effect of individual drugs in relation to their adverse effects when used as combination. Among the monotherapy group, amlodipine-induced pedal edema was the most common ADR noted (56.7%) followed by enalapril-induced dry cough (16.7%). This finding was supported by Beulah *et al.,* where the most common adverse effect observed was amlodipine-induced pedal edema (22%) and the second most common adverse reaction was ACE inhibitor-induced dry cough (10%) [34]. The relatively lower incidence of pedal edema in the CCB-thiazide groups as compared to CCB monotherapy could be attributed to the diuretic action of thiazides. Moreover, the incidence of adverse effects was more commonly seen in the amlodipine group possibly because it was the most common drug prescribed in the present study. Other adverse effects noted were electrolyte imbalances such as hyponatremia, hypokalemia, and hyperkalemia. No serious ADRs were observed in our study.

According to modified Hartwig severity scale, all ADRs were mild to moderate in severity which was managed by either reduction in dosage or frequency or change in the suspected drug, reduced dosage, or change in the drug [45]. According to the WHO causality assessment system**,** all these ADRs were classified as 'possible' because all ADRs occurred in relation to the time of drug intake, but which could be justified by other coexisting diseases or drugs [16].

Non-pharmacological therapy which includes alterations in the standard of living can reduce and thereby aid in BP adjustment. These prove to be appreciable when applied in support to drug therapy. It can play a critical role in controlling BP by improving the effectiveness of antihypertensive drugs, reducing the risks associated with the cardiovascular system, and also decrease the amount of drugs required or their dosage. Weight reduction in overweight or obese individuals [46], implementation of DASH eating plan rich in potassium, calcium, and dietary sodium reduction, and regular exercises [47-49] are some of the variations in daily life that have shown improved outcomes in BP reduction.

The major limitation of this study was the shorter duration of the study period. All patients were followed up for only 8 weeks. A longer duration of the study would have been helpful in a better understanding of the efficacy and tolerability of the drugs as it would have been essential in the better assessment of the various long-term cardiovascular and mortality outcomes. Hence, patients have to be followed for a longer period to evaluate the efficacy and tolerability of the drugs.

CONCLUSION

Though monotherapy and combination therapy were equally effective with the latter producing fewer ADRs, combination therapy may be considered as a better treatment option in selected patient population. However, further studies of longer duration are required to determine the long-term benefits of various antihypertensive medications used as both monotherapy and combination therapy for this chronic and diverse health problem.

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