Original Article

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Internal Medicine Section

Effectiveness and Safety of Fixed-dose Combination of Perindopril/Amlodipine/Indapamide, and Telmisartan/Amlodipine/Chlorthalidone in Grade 2 Hypertensive Patients at High Cardiovascular Risk: A Real-world Observational Study

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ABSTRACT

Introduction: Fixed-dose combination containing triple antihypertensive agents (Angiotensin-Converting Enzyme Inhibitor (ACE-I)/Angiotensin Receptor Blocker (ARB), diuretic and Calcium Channel Blocker (CCB) is recommended to achieve target Blood-Pressure (BP). However, none of the study has compared ACE-I based and ARB-based triple fixed dose combinations.

Aim: To evaluate the effectiveness and safety of fixed-dose combination of Perindopril (Per)/Amlodipine (Aml)/Indapamide (Ind) and Telmisartan (Tel)/Aml/Chlorthalidone (Chl) in grade 2 hypertensive patients at high Cardiovascular (CV) risk.

Materials and Methods: This retrospective, observational, single-centre study enrolled treatment-naïve grade 2 hypertensive patients who were at high CV risk and were treated with ACE-I based (Per/Aml/Ind group) or ARB-based (Tel/Aml/Chl group) triple fixed-dose combination for atleast one-month at the study centre. Office Blood Pressure (BP) at one-month follow-up was used as a parameter to measure treatment effectiveness. Safety was assessed based on the occurrence of Adverse Events (AEs).

Results: A total of 69 patients (n=32 in Per/Aml/Ind group and n=37 in Tel/Aml/Chl group) were included. Office Systolic BP (SBP)/Diastolic BP (DBP) were 181.44±8.52/95.19±7.25 mmHg and 183.32±6.65/94.81±7.14 mmHg in patients belonging to Per/Aml/Ind and Tel/Aml/Chl groups, respectively. There was a significant reduction in office SBP/DBP at one-month follow-up (Per/Aml/Ind: 129.31±6.44/75.06±4.85 mmHg and Tel/Aml/Chl: 129.10±5.90/75.00±4.82 mmHg; p-value=0.0001). Between-group comparisons did not showed any significant difference in terms of reducing office BP. Both groups exhibited identical safety profile.

Conclusion: The study demonstrated comparable treatment effectiveness and safety profile with triple fixed dose combinations containing Per/Aml/Ind and Tel/Aml/Chl in a real-world setting.

Keywords: Angiotensin-converting enzyme inhibitor, Angiotensin receptor blocker, Calcium channel blocker, Diuretic, Hypertension, Triple fixed-dose combination

INTRODUCTION

Hypertension is a major health burden worldwide with an estimated global prevalence of 1.5 billion by 2025 [1]. Among all CV risk factor, it is identified as the leading cause of mortality worldwide [2]. However, randomised controlled trials confirmed that effective BP lowering is associated with improved outcomes in terms of reduction of coronary heart disease, stroke, heart failure, CV death and all-cause death [3-5]. Hence, optimum BP control is of paramount importance. Several factors contribute to the development of hypertension, including increased circulating volume, sympathetic hyperactivity, increased total peripheral vascular resistance, and abnormal over-activity of the Renin Angiotensin Aldosterone System (RAAS) [6]. Hence, to control BP effectively, the concomitant administration of two or more antihypertensive medications from different pharmacological classes that target multiple pathways is necessary [7,8]. Notably, upto 60% patients fail to achieve target BP control with dual antihypertensive agents [9]. In this scenario, initiating hypertension treatment with triple fixed-dose combination seems a promising approach. Apart from proven safety and efficacy, fixed-dose combination therapy improves treatment adherence due to regimen simplification and thereby reduce patient, physician and healthcare system barriers related to multiple visits and prolonged titration schedules. Cost-effectiveness is another advantage of the fixed-dose combination therapy.

The ideal candidates for triple fixed dose combination include a RAAS inhibitor (ACE-I or ARB), a CCB and a diuretic. Among CCB, amlodipine is identified as the most-effective antihypertensive, either alone or in combination with other drug class [10]. While selecting diuretics, thiazide like diuretics (chlorthalidone and indapamide) is preferred over thiazide diuretics due to longer plasma half-life, neutral effect on metabolism and efficacy in preventing CV events [11]. However, the selection between ACE-I and ARB is challenging. From pathophysiological effects perspective, ACE-I seems superior as compared to ARB [10]. However, clinical studies reported controversial findings. Besides, as compared to ACE-I, ARBs have lower drug-related AEs leading to reduced rates of treatment discontinuation [10]. The safety and efficacy of the ACE-based and ARB-based triple fixed dose combinations in reducing BP has been well-established. Till date, no head-to-head study compares ARB-based and ACE-I-based triple fixed dose combinations. Hence, this study was designed to bridge this gap and report results using Per/Aml/Ind (an ACE-based triple fixed-dose combination)

and Tel/Aml/Chl (an ARB-based triple fixed-dose combination) in grade 2 hypertensive patients who were at high CV risk in routine clinical settings.

MATERIALS AND METHODS

A retrospective, observational, single-centre study was conducted at the Diabetes and Allergy-Asthma Therapeutics Specialty Clinic, Kolkata, West Bengal India, from November 2020 to February 2021. The data analysis was carried out after 15 days of study period. The study was approved by the Institutional Ethics Committee (IEC) (Human Research Ethics committee, Allergy and Asthma Research Centre, Kolkata; approval number: HREC-AARC/15) and was conducted in accordance with the regulatory requirements and Good Clinical Practice guidelines. The waiver for informed consent from the study participants was received from IEC.

Inclusion criteria: Patients on treatment-naïve and newly diagnosed grade 2 hypertensive patients with age ≥18 years who were at high CV risk, if they were prescribed single pill of fixed-dose triple combination of Per/Aml/Ind or Tel/Aml/Chl for atleast one month at the study centre. Treatment naïve newly diagnosed hypertensive patients with BP >160 mmHg or and >100 mmHg along, with any one risk factors like age (>65 years), sex (male>female), heart rate (>80 beats/min), obesity, diabetes, high Low Density Lipoprotein-Cholesterol (LDL-C)/triglyceride, family history of Cardiovascular Disease (CVD), family history of hypertension, early-onset menopause, smoking habits, psychosocial or socio-economic factors, having completed one month therapy in a therapeutics clinic.

Exclusion criteria: Patients whose one-month follow-up data was incomplete, were excluded from the study.

Data was recorded by the treating physician. Grade 2 hypertension was defined as SBP ≥160 mmHg and DBP ≥100 mmHg. The CV risk was calculated according to practice guideline of hypertension guidelines or the management of hypertension developed by International Society of Hypertension (ISH) [12].

Study Procedure

The patients were identified through online database of outpatients. The records were divided into two groups. The patients receiving a triple fixed-dose combinations of Per/Aml/Ind (5/1.25/5 mg or 5/1.25/10 mg or 10/2.5/5 mg or 10/2.5/10 mg) constituted the Per/Aml/Ind group, whereas patients receiving Tel/Aml/Chl (40/5/12.5 mg) constituted the Tel/Aml/Chl-group.

Patient medical records were examined retrospectively to collect all relevant data including demographics, CV risk factors, office SBP/DBP, and laboratory measurements at baseline and at one month. Information related to AEs was collected through verbal communication with the treating physician, patient and his/her caretaker. Data were collected using predefined case report form by a study coordinator.

STATISTICAL ANALYSIS

Categorical variables were presented as frequencies and percentages, and continuous variables were presented using mean ±standard deviation. Comparison was performed using paired t-test (within group), unpaired t-test (between two groups) or Chi-square test depending upon the types of variables. A p-value <0.05 was considered statistically significant. Statistical analysis was performed by using Statistical Analysis System (SAS).

RESULTS

From the database, data of 69 patients were included in this study. Of 69, 32 patients were in the Per/Aml/Ind group, and 37 patients in Tel/Aml/Chl group. The mean age of patients in Per/Aml/Ind and Tel/Aml/Chl groups was 57.06±7.51 years and 57.08±6.98 years, respectively. There was a statistically insignificant difference with respect to co-morbidities between both groups [Table/Fig-1].

Parameters	Per/Aml/Ind group (n=32)	Tel/Aml/Chl group (n=37)	p-value
Age, years (Mean±SD)	57.06±7.51	57.08±6.98	0.89
Gender, n (%)			
Female	14 (43.75)	13 (35.14)	0.47
Male	18 (56.25)	24 (64.86)	
Co-morbidities, n (%)			
Diabetes mellitus	24 (21.24)	31 (27.43)	0.37
Obesity	1 (0.88)	1 (0.88)	0.92
Dyslipidaemia	11 (9.73)	12 (10.62)	1.00
Benign prostate hyperplasia	1 (0.88)	1 (0.88)	1.00

[Table/Fig-1]: Demographics and baseline clinical characteristics of the study population.
p-values were obtained using either unpaired t-test or Chi-square test as applicable

For Per/Aml/Ind group, the mean office SBP decreased significantly from baseline to one-month follow-up (181.44±8.52 mmHg vs. 129.31±6.44 mmHg; p-value=0.0001). Similarly, mean DBP in this group decreased significantly from 95.19±7.25 mmHg at baseline to 75.06±4.85 at one-month follow-up. On the other hand, for the Tel/Aml/Chl group, mean office SBP reached 129.10±5.90 mmHg at one month follow-up from 183.32±6.65 mmHg at baseline , with a significant change at p-value=0.0001). Similarly, mean DBP for this group significantly reduced from 94.81±7.14 mmHg at baseline to 75.00±4.82 mmHg at one month follow-up (p-value=0.0001) [Table/Fig-2].

Blood pressure	Baseline	One-month	p-value[†]
Per/Aml/Ind group (n=32)			
Systolic blood pressure, mmHg (Mean±SD)	181.44±8.52	129.31±6.44	0.0001
Diastolic blood pressure, mmHg (Mean±SD)	95.19±7.25	75.06±4.85	0.0001
Tel/Aml/Chl group (n=37)			
Systolic blood pressure, mmHg (Mean±SD)	183.32±6.65	129.10±5.90	0.0001
Diastolic blood pressure, mmHg (Mean±SD)	94.81±7.14	75.00±4.82	0.0001

[Table/Fig-2]: Changes in systolic and diastolic blood pressures after one-month of treatment with (A) Per/Aml/Ind and (B) Tel/Aml/Chl.
[†]p-values were obtained using paired t-test

[Table/Fig-3] shows changes in biochemical/laboratory parameters at one-month follow-up from baseline. Mean change in creatinine levels was slightly higher in Tel/Aml/Chl group as compared to Per/Aml/Ind group, with statistically significant change observed for Tel/Aml/Chl group at p-value=0.0056. At one-month follow-up, there was a significant reduction (p-value=0.0030) in sodium

Biochemical parameters	Baseline	One-month	Change from baseline to one-month (95% confidence interval)	p-value
Per/Aml/Ind group (n=32)				
Creatinine, mg/dL (Mean±SD)	1.10±0.15	1.05±0.11	-0.05 (-0.095 to 0.002)	0.0574
Sodium, mEq/L (Mean±SD)	139.97±2.09	138.81±1.87	-1.1563 (-1.89 to -0.42)	0.0030
Potassium, mmol/L (Mean±SD)	4.10±0.22	4.09±0.22	-0.00938 (-0.09 to 0.07)	0.8185
Tel/Aml/Chl group (n=37)				
Creatinine, mg/dL (Mean±SD)	1.11±0.14	1.05±0.11	-0.0649 (-0.110 to -0.020)	0.0056
Sodium, mEq/L (Mean±SD)	140.05±2.22	136.43±5.86	-3.6216 (-5.66 to -1.59)	0.0009
Potassium, mmol/L (Mean±SD)	4.08±0.21	4.05±0.29	-0.0297 (-0.13 to 0.07)	0.5414

[Table/Fig-3]: Change in biochemical parameters after one month of treatment.
[†]p-values were obtained using paired t-test

level from 139.97±2.09 mEq/L at baseline to 138.81±1.87 mEq/L at one-month follow-up in Per/Aml/Ind group. Similarly, there was a significant (p-value=0.0009) reduction in sodium level from 140.05±2.22 mEq/L at baseline to 136.43±5.86 mEq/L in Tel/Aml/Chl group. Patients in the Tel/Aml/Chl group were likely to experience significant reduction in sodium level (p-value=0.0009). There was no significant change in potassium level in either group at one-month follow-up.

At one-month follow-up, there was no incidence of serious AE. In the Per/Aml/Ind group, reported AEs were occurrence of cough (n=2), dyselectrolyemia (n=1) and pedal oedema (n=2). No patient in Tel/Aml/Chl group experienced any incidence of cough. However, dyselectrolyemia and pedal oedema were noted in 7 and 2 patients in Tel/Aml/Chl group, respectively [Table/Fig-4].

Adverse event	Per/Aml/Ind group	Tel/Aml/Chl group	p-value[1]
Cough	2	0	0.2114
Dyselectrolytemia[2]	1	7	0.0602
Pedal oedema	2	2	1.0000

[Table/Fig-4]: Occurrence of Adverse Events (AE) during the study period.
[1]p-values were obtained using Chi-square test
[2]Dyselectrolytemia included hyponatraemia and hypokalaemia

DISCUSSION

Hypertension is a pressing global health issue. It is associated with increase in peripheral vascular resistance that, in turn, can lead to CV morbidities and mortality, if not identified early and treated properly. Triple fixed-dose combination of an ACE-I/ARB, diuretic and a CCB is recommended to treat uncontrolled hypertension by several guidelines [12-14]. Theoretically, these combinations possess several advantages: 1) combining RAAS inhibitor with diuretics produces additive effects on BP reduction; 2) improved tolerability profile of antihypertensive therapy i.e., RAAS inhibitor counteracts diuretic-induced adverse impacts on electrolytes, uric acid and glucose metabolism as well as CCB-induced peripheral oedema; 3) RAAS activation through combination of CCB and diuretics can be mitigated by adding RAAS-inhibitors [15]. Thus, combining these agents may prove beneficial to achieve target BP.

The selection between ACE-I and ARB seems a hard target to deal with. While ARBs have a more favourable tolerability profile, with lower rates of cough or angiooedema, clinical benefits are found higher with ACE-I than with ARB [16]. A meta-analysis assessing clinical benefits of ACE-I and ARB in 158,998 hypertensive patients from 20 contemporary hypertension trials demonstrated that the use of ACE-I was associated with reduction of all-cause mortality and CV mortality [17]. A meta-analysis involving diabetic patients found that ACE-I, but not ARB, reduced all-cause mortality, CV mortality, and major adverse CV events [18]. In contrast, the results of ONTARGET, the largest randomised controlled trial, reported equal efficacy of ACE-I (ramipril) and ARB (Tel) at reducing CV events and mortality in patients with CVD or high-risk diabetes [19]. An increasing number of evidence did not find any difference in efficacy between ARB and ACE-I at BP reduction, heart failure symptoms improvement and stroke reduction [20]. Intraclass variability in pharmacodynamic and pharmacokinetic properties in ARB class may also contribute to the inconsistency in therapeutic effects as well as clinical outcomes beyond BP control [20]. All the aforementioned findings/evidence was based on the trials involving each agent (ACE-I/ARB) alone. None of the study compared ACE-based and ARB-based triple fixed dose combination. Present study was designed to compare effectiveness and safety of ACE-based triple fixed dose combination and ARB-based triple fixed dose combination.

Results of the present study confirmed effectiveness and safety of both triple fixed-dose combinations containing Per/Aml/Ind and Tel/Aml/Chl from the outpatient database of treatment-naïve grade 2 hypertensive patients who were at high CV risk. Both, ACE-I based and ARB based single pill fixed-dose combinations, were effective in reducing office BP without any clinically significant interference in biochemical parameters at one-month follow-up. At one-month follow-up, the reduction in SBP and DBP in patients treated with ACE-based triple fixed dose combination was found to be 52.13 mmHg and 20.13 mmHg, respectively. For patients receiving ARB-based triple fixed dose combination, the reduction in SBP and DBP was 54.24 mmHg and 19.81 mmHg, respectively. Present study found non significant difference in reduction in SBP and DBP between two fixed dose combinations that could be attributed by small sample size. There were no incidences of serious AEs.

The reductions in BP observed in the present study were consistent with other studies [21-28]. The Per/Aml/Ind is the most extensively evaluated triple fixed dose combination. Randomised double-blind, controlled trials demonstrated significant BP reduction with triple fixed dose combination containing Per/Aml/Ind as compared to dual antihypertensive therapy in different subgroup of hypertensive patients [29,30]. The 'Perindopril-Amlodipine plus Indapamide Combination for Controlled Hypertension—Non Intervention Trial' (PAINT) study which included 6088 patients with uncontrolled hypertension demonstrated significant BP reduction (SBP/DBP: 26.7±13.3/12.9±9.4 mmHg; p=0.001) with Per/Aml/Ind at 4-month follow-up [27]. The findings of 'Perindopril-Indapamide plus Amlodipine in High Risk Hypertensive Patients' (PIANIST) study extended safety and effectiveness of this single-pill triple fixed-dose combination in hypertensive patients (N=4731) who were at high or very high CV risk [28]. The SBP/DBP reduction was found to be 28.3±13.5/13.8±9.4 (p=0.0001) after 4-month therapy with Per/Aml/Ind. Thacker H et al., demonstrated BP reduction of 28.5/13.8 mmHg in patients with uncontrolled hypertension in Indian scenario [31].

Other real-world studies also demonstrated BP-lowering effectiveness and safety of Per/Aml/Indin a large pool of hypertensive patients [26-32]. Similarly, efficacy and safety of ARB-based study have been confirmed in several studies. Randomised controlled trial evaluating effectiveness of ARB-based triple therapy with Aml, Valsartan (Val) and hydrochlorthiazide (HCTZ) (10/320/25 mg) in patients with BP ≥145/100 mmHg showed significant reductions in SBP/DBP of 39.7/24.7 mmHg at 8 week follow-up [22]. A randomised controlled trial, 'Triple Therapy with Olmesartan Medoxomil, Amlodipine and Hydrochlorothiazide in Hypertensive Patients Study' (TRINITY), showed reduction of 37.1/21.8 mm Hg in SBP/DBP with the ARB-based triple therapy at 12-week follow-up [24]. Triple antihypertensive therapy containing Aml/Tel/HCTZ (5/40/12.5 mg) found efficacious in reducing BP in patients with moderate to severe hypertension [23]. The effectiveness of ARB-based triple therapy at reducing BP has been confirmed in real world setting also [21,25-28]. Of note, while the effectiveness of the ARB-based triple therapy is awaited, ACE-based triple therapy shows substantial reduction in CV risk using Per/Aml/Ind [33]. The trials and real-world studies demonstrate similar tolerability profiles with ACE-based and ARB-based triple fixed dose combinations [15].

Limitation(s)

The study possesses inherent limitations of an observational study and small-sized treatment groups were another major limitation. Though the effectiveness of antihypertensive medications can be assessed accurately through ambulatory BP monitoring, which could not be performed in this study. Furthermore, the impact of lifestyle changes or adherence to antihypertensive medications was not assessed. Despite these limitations, the results of the study provide an evidence of safety and effectiveness of single-pill fixed-dose triple combinations of antihypertensive medications in routine clinical practice.

CONCLUSION(S)

Results derived from the data for the present study provides strong evidence for safety and effectiveness of fixed-dose

triple combinations containing Per/Aml/Ind and Tel/Aml/Chl in treatment-naïve hypertensive patients in a real-world scenario. The combinations were well tolerated and no incidences of serious AEs were reported. However, a large-scale study may be needed to reiterate long-term safety and clinical outcomes of these triple fixed dose combinations.

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