

ORIGINAL ARTICLE

Evaluation of Clinical Acceptability of Perindopril / Indapamide Single-pill Combination in Moderate to Severe Hypertension

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Abstract

Background: Current European hypertension guidelines recommend to initiate the treatment of patients with moderate to severe hypertension with a Single Pill Combination (SPC) containing two drugs, as SPC use leads to more effective and faster blood pressure control. The guidelines also recommend tighter blood pressure control in hypertensive patients with cardiovascular risk factors such as diabetes mellitus.

Objective: To evaluate efficacy on blood pressure reduction and acceptability of the single pill combination of Perindopril/Indapamide in patients with moderate to severe hypertension.

Methods: In this multicentre, prospective, observational study, patients with moderate to severe hypertension were prescribed Perindopril 4mg/Indapamide 1.25 mg for 90 days. The primary outcomes were blood pressure decrease and achievement of BP control. Patients were up-titrated to Perindopril 8 mg/Indapamide 2.5 mg SPC, if target BP control ($\leq 140/90$ mm Hg) could not be achieved by day 30.

Results: In this study, 173 hypertensive patients, with a mean age of 51 years were enrolled at 3 centres from different geographic areas within India. Mean SBP/DBP decreased significantly from baseline (155.70 (± 10.39) / 95.72 (± 6.99) mmHg) over 90 days (30.31 (± 14.15) / 17.14 (± 9.33) mmHg; $p < 0.0000$). Few side effects were reported during the 90-day period.

Conclusion: Perindopril/Indapamide given as a SPC was found to be an effective and well-tolerated antihypertensive combination resulting in rapid blood pressure control in patients with moderate to severe hypertension.

Introduction

Hypertension plays a major role in the development of cerebrovascular disease, ischemic heart disease, cardiac and renal failure. Treating hypertension has been linked with about 40% reduction in the risk of stroke and about 15% reduction the risk of myocardial infarction. Although the treatment for hypertension has been shown to prevent cardiovascular disease and to increase life expectancy, hypertension remains inadequately controlled.^{1,2}

Based on the available clinical evidence today the algorithm of hypertension treatment pertains to age and ethnic background. The ESC/

ESH 2013 as well as 2018 guidelines recommend to commence the two drugs therapy in patients with moderate to severe hypertension (Systolic BP above 160 mmHg and/ or Diastolic BP above 100 mmHg). The guidelines suggests tighter blood pressure control in patients with cardiovascular risk factors such as patients with diabetes mellitus.³⁻⁵

This study examines the efficacy, in terms of blood pressure control, and acceptability of Perindopril/

Indapamide SPC in moderate to severe hypertensive patients.

Materials and Methods

Study Design

This study was an open-label, Multicentric, Non-comparative Phase IV study in patients with moderate to severe hypertension. The study protocol was approved by the Indian regulatory authorities and registered on the clinical trial registry of India (CTRI/2017/07/009160). The study was conducted in accordance with the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. Written informed consent was obtained from all patients before participation in the study.

The study aimed to evaluate the clinical efficacy and acceptability of the Perindopril/Indapamide SPC. The recommended initiation dose of Perindopril 4 mg /Indapamide 1.25 mg) was administered to all eligible subjects in the morning for 90 days. The study protocol included an up-titration step to Perindopril 8 mg/Indapamide 2.5 mg at visit 3 (Day 30) when the blood pressure response achieved was inadequate with the initiation dose of a Perindopril 4 mg + Indapamide 1.25 mg. The target for BP control was set by Principal investigator based on patient's health profile, co-morbid health issues and risk factors however control rate of the BP was considered as $\leq 140/90$ mm Hg.

Selection of patients

To be enrolled in the study, patients had to be diagnosed with hypertension (grade II or above) and aged between 18 and 65 years, either newly diagnosed patients with baseline blood pressure

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Table 1: Baseline characteristics (ITT)

i. Total number of patient population	N= 173
ii. Age, years \pm SD	50.96 \pm 9.22
iii. Men, n (%)	96 (55.5%)
iv. Cardiovascular risk:	
a. Current smokers	05
b. Current alcohol consumption	11
c. Weight, kg \pm SD	72.42 \pm 12.10
d. BMI, kg/m ² \pm SD	26.6 \pm 4.16
e. Diabetes, n (%)	106 (61.27%)
f. Dyslipidaemia, n (%)	66 (38.15%)
g. Hypothyroidism, n (%)	17 (9.82%)
h. IHD, n (%)	2 (1.15%)
i. Other, n (%)	11 (6.35%)
v. Systolic blood pressure, mmHg \pm SD	155.70 \pm 10.39
vi. Diastolic blood pressure, mmHg \pm SD	95.72 \pm 6.99
vii. Heart Rate, bpm \pm SD	81.84 \pm 7.93

(SBP/DBP) > 160/100 mmHg or treated patients uncontrolled (baseline SBP/DBP >140/90 mmHg) by monotherapy or two drug therapy of antihypertensive medication. Exclusion criteria were history of myocardial infarction, cerebrovascular event, uncontrolled arrhythmias, uncontrolled diabetes (HbA1C more than 7%), history of heart failure, severe impaired renal function and/ or serious liver disorders, history of hypersensitivity to Perindopril or Indapamide, receiving beta blockers for hypertension, having contraindications for Angiotensin Converting Enzyme (ACE) I and/ or Thiazide type diuretic, pregnancy or lactation, and any other condition or disease that may preclude evaluation of study medication as per investigator's opinion.

Study assessments & Follow up

The study aimed to evaluate the blood pressure reduction from baseline to the end of study with treatment with Perindopril/Indapamide SPC and the proportion of patients achieving target BP control \leq 140/90 mmHg. For diabetic patients the target blood pressure control was \leq 140/85 mmHg as per ESH/ESC 2013 guidelines. Safety assessment was the secondary endpoint and included assessment of tolerability and acceptability of the treatment in terms of incidence of side effects and treatment compliance. The trial was carried out in an out-patient setting; the study design included screening visit, study inclusion and treatment initiation visit (D0) and follow-up visits at Day 15, Day 30, Day 60 and end of study visit at Day 90. At each visit the investigator assessed any incidence

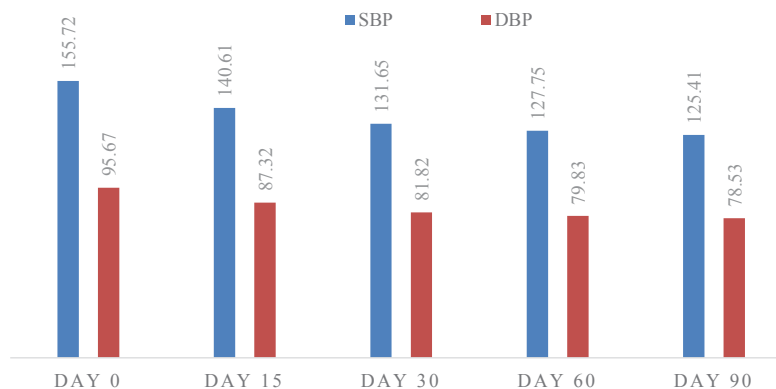


Fig. 1: Blood pressure response to treatment with Fixed dose Combination of Perindopril + Indapamide in moderate to severe hypertension (mm Hg)

of adverse events experienced by the patients. The physician also at his / her discretion decided treatment continuation and / or discontinuation in case of inadequate blood pressure control observed with the highest dose in the patient. The global assessment of the study medication in terms of efficacy and tolerability was rated by the physicians at the end of the study. The treatment compliance was assessed by interviewing the patients, return of unused medication and review of patient diaries.

Statistical analysis

The statistical analysis consisted on descriptive statistics as well as the evaluation of end points. SPSS version 24 was used. The primary endpoints were mean change in blood pressure from baseline to end of the study after receiving the study treatment and the number of patients achieving blood pressure control (SBP < 140 and DBP < 90 mmHg, including those with diabetes) on an intention to treat basis. Other outcomes were frequency of side effects reported by the patient and adherence with the study treatment. Significance was defined as a p value of less than 0.05.

Results

Patient population

A total of 181 patients were screened out of which 173 patients were enrolled in the study, across 3 study centers in India. 133 patients completed the study as per the protocol. Baseline characteristics of study population are shown in Table 1. At baseline, mean age was 50.96 years (\pm 9.22), 55.5% of patients were male, with 61% had diabetes mellitus and 38%

had dyslipidemia as a co-morbid condition.

Primary efficacy analysis: Blood pressure response to treatment

Treatment with Perindopril/Indapamide SPC led to a reduction in SBP by 15.11 mmHg and in DBP by 8.35 mmHg at Day 15 compared to baseline. At Day 30, further significant reduction was observed in SBP by 8.96 mmHg and in DBP by 5.50 mmHg compared to day 15. At the final study visit (Day 90), statistically highly significant (p value: 0.000 student t-test) reduction in blood pressure from baseline SBP 30.31 (14.151)/DBP 17.14 (9.336) mmHg was observed. Mean SBP/DBP values decreased from 155.7 \pm 10.39/95.7 \pm 6.99 mmHg at baseline to 131.65 \pm 10.53 / 81.82 \pm 7.79 mmHg at day 30 and to 125.4 \pm 9.072 / 78.5 \pm 7.713 mmHg at day 90 (Figure 1). Mean heart rate decreased from 81.57 \pm 7.93 at baseline to 79.45 \pm 6.61 bpm at day 30 and to 78.90 \pm 7.83 at day 90. The SPC of Perindopril/Indapamide was found to be effective in more than 90% of the patients recruited in the study. 127 patients achieved blood pressure control (SBP less than 140 mmHg and DBP less than 90 mmHg, including those with diabetes) after 90 days.

Withdrawals and up-titration

Out of 181 screened patients, 173 were enrolled and 133 patients completed the study being adherent to protocol schedule and treatment.

The up-titration of the study medication was required in 14 patients; they were up-titrated to the SPC of Perindopril 8 mg/Indapamide 2.5 mg at Visit 3. All these patients achieved target blood pressure control following the up-titration (reviewed at day 5 following the ingestion of higher dose)

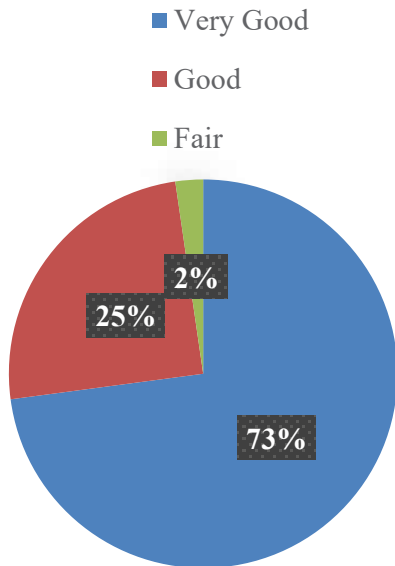


Fig. 2: Study treatment efficacy

without any further change in treatment line and the same treatment was continued. Seven patients discontinued the study for various reasons such as difficulties to follow up and personal decision. None of the patients were withdrawn due to adverse events. The global assessment by the investigators rated the efficacy of the treatment as very good (73%) and tolerance (95%) at the end of the study (Figures 2 and 3).

Safety analysis

During the entire study period, a total of nine adverse events were reported such as dry cough, headache, high fever, gastroesophageal reflux disease, giddiness, and paronychia. Adverse events were mild in severity and not related to SPC (perindopril + indapamide) and all resolved during the study period. The laboratory parameters remained within the normal range and the study treatment had no impact on the laboratory parameters particularly the electrolytes. None of the patients had any signs and symptoms of hyponatremia and/ or, hypokalemia and any other electrolytes imbalances and as confirmed by the lab investigations.

Discussion

It is usual practice to add 1-2 sentences at the beginning of discussion, summarising the main findings of the study.

Recent epidemiological data reveals prevalence of hypertension in 25–30% urban and 10–20% rural

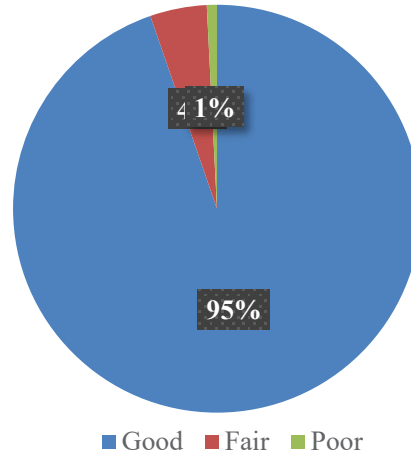


Fig. 3: Study treatment tolerance

subjects in India. This translates into 100–110 million persons with this condition in the country. Hypertension is classified as Category 3 (specific factors) risk factors for disease burden (disability adjusted life years) and mortality in India as per the Global Burden of Disease Study 2015.⁶ It is well understood that hypertension management and control is crucial to prevent its vascular complications.⁷ There is strong evidence from clinical trials and meta-analyses of systolic blood pressure > 140 mmHg being harmful and prompt initiation and titration of therapy to achieve and maintain systolic blood pressure < 140 mmHg is recommended. A meta-analysis reported that each 10 mmHg reduction of systolic blood pressure was associated with significantly lower risk of mortality, cardiovascular events, coronary heart disease, stroke, albuminuria and retinopathy in patients with hypertension.⁸ Strong evidence also exists from randomised clinical trials that systolic blood pressure < 130 mmHg and diastolic blood pressure < 90 mmHg is associated with decreased adverse vascular complications.²

Using two-drug SPCs is one of the key recommendations of latest guidelines on hypertension ESC/ESH 2018 especially when the monotherapy is inadequate to achieve target range of BP control in moderate to severe hypertensive patients as well as grade 1 patients with risk factors.⁹ The exceptions to these recommendations are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg). This strategy also enhances adherence to BP-lowering medication contributing

to higher rates of reduction in blood pressure.¹⁰

The present phase IV study considered a wide spectrum of hypertensive patient population ranging from grade II to grade III hypertensive patients who were inadequately managed on monotherapy or any other two drug combinations. Few of the included patients presented some other comorbid conditions. The target BP for patients receiving treatment was < 140/90 mmHg for patients with hypertension alone whereas a tighter BP control (< 140/85 mm of Hg) was expected in hypertensive patients with history of diabetes mellitus.⁸ Approximately, 60% of study population had co-morbid conditions like diabetes mellitus (60%) and dyslipidaemia (38%).

While planning a treatment algorithm for such wide range of hypertensive population, a single pill combination of an ACE inhibitor (Perindopril) and thiazide like diuretic (Indapamide) should be considered as first line treatment in clinical practice.¹¹ The single-pill combination of Perindopril/Indapamide leads to additive synergistic action on vascular endothelium, arteriocapillary microcirculation and the target organs of hypertension and thus helps in gradual but definite achievement of target BP control.^{12,13} The clinical assessments of present study confirmed efficacy of Perindopril + Indapamide in more than 90% of study population with lower dose of SPC after 90 days. Less than 10% of the study population (n=14) required an up-titration to Perindopril 8 mg/Indapamide 2.5 mg during the study period and all these patients achieved target blood pressure without addition of any other new drug. Reduction in the heart rate in consequence to the reduction in blood pressure was also observed. The study medications demonstrated satisfactory safety profile.

The study treatment was rated by investigators for global evaluation parameters like Treatment efficacy, Treatment tolerance, Treatment compliance and Patient's satisfaction with treatment. The study results demonstrated coherent acceptance of this SPC by investigators as well as the patients.

The beneficial effects of combination of Perindopril and Indapamide in

reducing blood pressure have been demonstrated in many trials and meta-analysis.¹⁴ A meta-analysis involving 3 large randomized controlled trials conducted with fixed combination of Perindopril 4 mg and Indapamide 1.5 mg concludes significant reduction of vascular death and major cardiovascular events.¹⁵

Recommendation of fixed combination of Perindopril + Indapamide has been confirmed in Diabetic hypertensive patients through a detailed meta-analysis.¹⁶ Perindopril being an ACE inhibitor class of drug imparts cardioprotective and nephroprotective effects in hypertensive patients.^{17,18} The study results with this SPC are similar to the reported data in the literature. The available clinical literature and recommendations from all the guidelines support use of Perindopril and Indapamide as the drugs for the treatment of hypertension. This recommendation is based on the established clinical efficacy and safety of these two drugs in monotherapy as well as in combination treatment. Although the number of patients requiring higher dose has been limited, the clinical efficacy and acceptability is well demonstrated and reconfirmed among the Indian patients.

Conclusion

This observational study showed that treatment with Perindopril/Indapamide SPC reduced BP rapid and significantly, resulting in high rates of BP control, and was well tolerated in patients with moderate to severe hypertension,

newly diagnosed or uncontrolled on monotherapy or combination therapy, in daily clinical practice.

Acknowledgement

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Conflicts of Interest

The study was sponsored by Serdia Pharmaceuticals (India) Pvt. Ltd. Mumbai. Dr. G. Jabre, S. Joseph and Dr. M. Rajarshi are employees of Serdia Pharmaceuticals. All other authors have no conflicts of interest to declare. Editorial assistance and article processing charges were funded by Serdia Pharmaceuticals (India) Pvt. Ltd. Mumbai.

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