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Original Research Article

A prospective and open label study of use of cilnidipine and chlorthalidone fixed dose combination in Indian hypertensive patients, intolerant or uncontrolled on amlodipine and hydrochlorothiazide combination

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ABSTRACT

Background: Primary aim of this study was to evaluate the antihypertensive efficacy of the Cilnidipine and Chlorthalidone fixed dose combination in Indian hypertensive patients who are not controlled on traditionally used amlodipine and hydrochlorothiazide combination and also to evaluate the safety of this combination.
Methods: A total of 70 eligible patients were enrolled in this prospective, open label study. The patients were given cilnidipine (10 mg) and chlorthalidone (12.5 mg) who had not achieved target blood pressure (140/90 mmHg) despite on amlodipine (5 mg) and hydrochlorothiazide (12.5mg) combination or are intolerant to the medication. The assessment was done at the end of 4 weeks and 8 weeks.
Results: There were significant falls in the SBP (5.43±2.45 mmHg, P<0.05), and DBP (4.11±2.35 mmHg, P<0.05) at the end of 4 weeks as compared to those at the baseline. The trend was sustained at 8 weeks. No further significant fall in the SBP and DBP were noted after 4 weeks (5.43±2.45 and 5.22±2.38 mmHg at 4 weeks vs 4.11±2.35 and 4.01±2.23 mmHg at 8 weeks P=NS). The SBP target (140 mmHg) was achieved in 25 patients (35.71%). The DBP target (90 mmHg) was achieved in 18 patients (25.71%). The combined SBP and DBP target was achieved in 12 patients (17.14%). A similar fall in the SBP was observed in the subgroups which were analysed.
Conclusions: The hypertensive patients who do not achieve the target blood pressures on amlodipine and hydrochlorothiazide can be switched to the cilnidipine and chlorthalidone combination. The combination is effective and well tolerated.

Keywords: Amlodipine, Cilnidipine, Chlorthalidone, Hypertension, Hydrochlorothiazide

INTRODUCTION

Hypertension is a major risk factor for all cardiovascular events. Of a number of risk factors that have to be directly responsible for the increase in cardiovascular morbidity and mortality, high blood pressure (BP) is one of the most important and independent risk factor, affecting 24 to 36 % of the adult population in developed countries.[1] Epidemiological studies have established a strong and linear relationship between BP and cardiovascular disease and randomized trials have documented that BP reductions by antihypertensive drugs confer cardiovascular protection.[2]

In patients aged >55 years, most of the guidelines recommend calcium channel blockers (CCB) as first line

drugs.[3-6] CCBs mainly act by vasodilatation and reduction in peripheral vascular resistance. They are the most commonly used drugs for the management of systemic hypertension. CCBs are a heterogeneous group of drugs that can chemically be classified into dihydropyridines (DHPs) non dihydropyridines (non-DHP). Their common pharmacologic property is selective inhibition of L-type calcium channel opening in vascular smooth muscle and in myocardium. DHP agents have more vascular selectivity than non-DHP. Nifedipine, the prototypical DHP can be considered as first-generation agent. It has no effect on the N-type calcium channels. The immediate release preparation produces profound vasodilatation and reflex tachycardia due to sympathetic stimulation. The plasma norepinephrine levels are increased. These effects are partly alleviated by slow release formulations. DHPs like Benidipine, Efinidipine, and Nitrendipine are categorized as second-generation agents and they induce vasodilatation action more slowly than nifedipine. Amlodipine and Azeldipine are classified as third generation agents. Amlodipine has a unique pharmacokinetic profile with slow onset of action and t1/2 of almost 36 hours.

Cilnidipine is a novel and unique 1, 4-DHP derivative developed in Japan. It is a dual action CCB with action on both L/N type of calcium channels, has been included in the list of first line antihypertensive agents by the Chinese guidelines for the prevention and treatment of patients with hypertension in 2009.[7-10] Several Chinese studies have established efficacy and safety of cilnidipine primarily in Chinese patients.[11-15] A meta-analysis by Guoliang et al have suggested that cilnidipine is equally effective and safe compared to amlodipine.[16] Cilnidipine is safe and effective in reducing low grade albuminuria in Indian patients with hypertensive chronic kidney disease.[17] Sagarad et al have reported safety and efficacy of cilnidipine in Indian hypertensive patients.[18] Recently replacement of amlodipine with cilnidipine has been shown to reduce pedal edema.[19,20]

Among other anti-hypertensive drugs, the thiazide type diuretics confer a significant reduction in cardiovascular events.[21-27] Their strong record of evidence, low costs and tolerability have made the low dose thiazide like diuretics the initial therapy in most of the anti-hypertensive regimens.[28] However, many of the pivotal studies have used chlorthalidone as the initial therapy, believing that it has a longer duration of action.

A longer duration of action provides a night time BP control and hence, it is effective in providing additional protection from stroke and myocardial infarction, which was shown by Earnst et al.[29,30] In a study by Lund and Earnst, a real-world experience of effectiveness of chlorthalidone and hydrochlorothiazide, it supported the potential efficacy advantage of chlorthalidone among the patients who tolerated the drug and remained persistent with the treatment.[31]

A majority of the hypertensive patients cannot be controlled by using one drug. JNC 7 as well as the European Society of Hypertension and Cardiology and the German Hypertension league, have stated that a large proportion of hypertensive patients will require a combination of two or more antihypertensive agents to achieve the desired target BP.[28,33-35]

This study was aimed to evaluate the efficacy of fixed dose combination of cilnidipine and chlorthalidone in patients who are uncontrolled or intolerant to fixed dose combination of amlodipine and hydrochlorothiazide as it is not reported earlier.

METHODS

The prospective and open label study was conducted at Rajiv Gandhi Super Speciality Hospital, Raichur Institute of Medical Sciences, Raichur from November 2014 to January 2016.

Hypertensive patient's male and female above 18 years attending OPDs / Clinics of the investigators were included in the study. Uncontrolled BP was defined has systolic BP > 140 mmHg and diastolic BP > 90 mmHg despite on a fixed dose combination of Amlodipine and hydrochlorothiazide.

Patients with severe co-morbidities (renal failure, hepatic failure, known malignancies with limited life expectancy, recent acute medical illness requiring hospitalization) were excluded from study. Also, patients with severely uncontrolled BP and ongoing evidence of organ dysfunction were excluded.

All patients were switched to a fixed dose combination cilnidipine and chlorthalidone and observed at the end of 4 weeks and 8 weeks. BP is recorded as per standard protocol at base line at the end of 4 weeks and 8 weeks. All patients were enquired for any side effects during the study period. All other drugs were allowed to continue as per the discretion of the investigator depending on the co-morbidities. All study participants were advised to avoid over the counter drugs during study period.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki and ethical committee clearance was taken.

Statistical analysis

The primary objective behind the assessment of the efficacy was to compare the mean falls in SBP and DBP after 4 and 8 weeks after the treatment change. The basic descriptive statistics were calculated and expressed as ±SD. The data at baseline and at 4 weeks and 8 weeks was compared by using t tests with a level of significance of 0.05. The statistical analysis was carried out with Minitab 16.

RESULTS

During the study period (Table 1), totally 70 patients were enrolled (40 males and 30 females). A majority were middle aged (55.66±9.07, range 40 to 70) patients. Diabetes was present in 20 (28.57%) patients. Known coronary artery disease in 20 (28.57%) patients. Current smoking was noted in 15 (21.4%). All patients had received the amlodipine and hydrochlorothiazide for more than 4 weeks. 10 patients were intolerant to the combination (pedal edema, giddiness, headache, weakness) and preferred to change medications.

Table 1: Baseline characteristics.

Age (mean ± SD), years	55.66±9.07
Sex	M (40):F(30)
Diabetes (N, %)	20 (28.57%)
CAD (N, %)	20 (28.57%)
Current smoking (N, %)	15 (21.4%)
SBP (mean ± SD) mmHg	155.78±3.77
DBP (mean ± SD) mmHg	98.75±2.55

The SBP and the DBP were 155.78±3.77mmHg and 98.75±2.55 mmHg at baseline (Table 2). At 4 weeks the SBP and the DBP were 144.45±5.15 and 94.15±4.21mmHg respectively.

Table 2: Comparison of SBP and DBP fall (mmHg, mean±SD).

SBP (Baseline vs 4 weeks, all patients)	155.78±3.77 vs 144.45±5.15, P<0.05
DBP (Baseline vs 4 weeks, all patients)	98.75±2.55 vs 94.15±4.21, P<0.05
SBP (Male vs Females, after 4 weeks)	5.39±2.87 vs 5.22±2.79, P=NS
SBP (Diabetics vs Non-diabetics, after 4 weeks)	5.50±2.80 vs 5.44±2.77, P=NS
SBP (Smokers vs non-smokers, after 4 weeks)	5.41±2.77 vs 5.33±2.69, P=NS
DBP (Male vs Females, after 4 weeks)	4.10±2.43 vs 4.12±2.45, P=NS
DBP (Diabetics vs Non-diabetics, after 4 weeks)	4.22±2.55 vs 4.11±2.39, P=NS).
DBP (Smokers vs non-smokers, after 4 weeks)	4.22±2.46 vs 4.19±2.55, P=NS),

There were significant falls in the SBP (5.43±2.45 mmHg, P<0.05), and DBP (4.11±2.35 mmHg, P<0.05) at the end of 4 weeks as compared to those at the baseline. The trend was sustained at 8 weeks. No further significant fall in the SBP and DBP were noted after 4 weeks (5.43±2.45 and 5.22±2.38 mmHg at 4 weeks vs 4.11±2.35 and 4.01±2.23 mmHg at 8 weeks P=NS). The SBP target (140 mmHg) was achieved in 25 patients (35.71%). The DBP target (90 mmHg) was achieved in 18 patients (25.71%). The combined SBP and DBP target was achieved in 12 patients (17.14%).

A similar fall in the SBP was observed in the subgroups which were analyzed (Table/Fig 2), like in male's vs females (5.39±2.87 vs 5.22±2.79 mmHg, P=NS), smoker's vs non-smokers (5.41±2.77 vs 5.33±2.69 mmHg, P=NS), and diabetics vs non-diabetics (5.50±2.80 vs 5.44±2.77 mmHg, P=NS).

Similar results were also observed in DBP fall among the subgroups, like male's vs females (4.10±2.43 vs 4.12±2.45 mmHg, P=NS), smoker's vs non-smokers (4.22±2.46 vs 4.19±2.55 mmHg, P=NS), diabetics vs non-diabetics (4.22±2.55 vs 4.11±2.39 mmHg, P=NS).

All patients tolerated the cilnidipine and chlorthalidone combination. No patient did withdraw from this combination. Mild pedal edema persisted in 2 patients who had experienced it with amlodipine and hydrochlorothiazide combination. No new onset pedal edema reported during study period.

DISCUSSION

Epidemiological studies have established a strong and linear relationship between BP and cardiovascular disease and randomized trials have documented that BP reductions by antihypertensive drugs confer cardiovascular protection.[2]

Many different classes of drugs are available to reduce BP. Mainly ACE inhibitors, ARBs, CCBs, Diuretics and beta blockers are the main class of drugs which are generally recommended by various guidelines. [28,32,33,36,37]

Among CCBs amlodipine is the most widely used third generation agent. It has a unique pharmacokinetic profile with slow onset of action and t1/2 of almost 36 hours. Reflex stimulation of the sympathetic nervous system is significantly less compared with previous generation DHPs. No effects on the N-type channels have been demonstrated. Data from 40 placebo controlled studies showed ankle edema as a common side effect (9.8% vs 2.3% P<0.001) and appears to be a reason for withdrawal. Headache, tiredness, vertigo, nausea and flush are other reported side effects.[34]

Cilnidipine is a novel dual action CCB with action on both L/N type of calcium channels, has been included in the list of first line antihypertensive agents by the Chinese guidelines for the prevention and treatment of patients with hypertension in 2009, several Chinese studies have established efficacy and safety of cilnidipine primarily in Chinese patients.[7-15]

A meta-analysis by Guoliang et al have suggested that cilnidipine is equally effective and safe compared to amlodipine.[16] Cilnidipine is safe and effective in reducing low grade albuminuria in Indian patients with hypertensive chronic kidney disease.[17] Sagarad et al have reported safety and efficacy of cilnidipine in Indian hypertensive patients.[18]

Among other anti-hypertensive drugs, the thiazide type diuretics confer a significant reduction in cardiovascular events.[21-27] Their strong record of evidence, low costs and tolerability have made the low dose thiazide like diuretics the initial therapy in most of the anti-hypertensive regimens.[28]

However, many of the pivotal studies have used chlorthalidone as the initial therapy, believing that it has a longer duration of action. A longer duration of action provides a night time BP control and hence, it is effective in providing additional protection from stroke and myocardial infarction, which was shown by Earnst et al.[29,30]

In a study by Lund and Earnst, a real-world experience of effectiveness of chlorthalidone and hydrochlorothiazide, it supported the potential efficacy advantage of chlorthalidone among the patients who tolerated the drug and remained persistent with the treatment.[31]

In this study demonstrated that those patients who are on amlodipine and hydrochlorothiazide combination and if their BP is not controlled or are intolerant to the combination can be safely shifted to combination of cilnidipine and chlorthalidone. This new combination is found to be safe and effective.

In the current study there were significant fall in SBP and DBP at 4 weeks compared to baseline. This trend was sustained at 8 weeks. The SBP target (140 mmHg) was achieved in 25 patients (35.71%). The DBP target (90 mmHg) was achieved in 18 patients (25.71%).

The combined SBP and DBP target was achieved in 12 patients (17.14%) over and above what the combination of amlodipine and hydrochlorothiazide had achieved. The results were seen across different spectrum of patients (male vs females, smoker's vs non-smokers, diabetics vs non-diabetics).

Also encouraging fact to recommend the new combination is lack of significant side effects which is consistent with earlier report.[18] None our patients discontinued the medications due to side effects which is consistent with earlier reports.[19,20]

Limitation of the study was to has similar limitations as that of any open label trials. Ideally a double blind randomized controlled trial is needed to confirm the results. Ambulatory BP monitoring is a better modality which can be used to assess the 24 hours BP reduction effects of the anti-hypertensives, which was not done in this study.

CONCLUSION

The results of this study demonstrated that the combination of cilnidipine and chlorthalidone was effective in the patients who remained uncontrolled after being on the amlodipine and hydrochlorothiazide combination. A significant proportion of the patients can achieve the target BP without having to face any clinically significant adverse events. Cilnidipine and chlorthalidone is a useful combination before dose escalation or addition of a third agent. Larger and long-term studies are needed to confirm and document long term safety and cardiovascular benefits of this new combination.

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