Original Article

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Pharmacology Section

Comparative Study of High Dose Mono-Therapy of Amlodipine or Telmisartan, and Their Low Dose Combination in Mild to Moderate Hypertension

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ABSTRACT

Introduction: Hypertension is one of the major public health challenges worldwide. Angiotensin receptor blockers (ARBs) and Calcium channel blockers (CCBs) are among the first line antihypertensive drugs. However, optimal treatment strategies in mild to moderate hypertensives who failed to achieve blood pressure (BP) control with low-dose mono-therapy are not well established. This study was done to compare efficacy and safety of high dose mono-therapy of Amlodipine, Telmisartan and their low dose combination in mild to moderate hypertensives who failed to achieve BP control with low dose mono-therapy of either drug.

Materials and Methods: A total of 96 patients, fulfilling inclusion and exclusion criteria were enrolled in the study after obtaining informed consent. Patients were randomized into three treatment groups i.e. Telmisartan 80 mg, Amlodipine 10 mg and low dose combination of Telmisartan 40 mg +Amlodipine 5 mg once daily for two months. The systolic BP, Diastolic BP, and ADRs were recorded at 0, 2, 4, 8 weeks.

Results: In the present study, significant reduction of mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) was seen in all the three treatment groups. Low dose combination of Amlodipine 5 mg and Telmisartan 40 mg showed statistically significant reduction in SBP as compared to Telmisartan 80 mg mono-therapy and in DBP as compared to Amlodipine 10 mg mono-therapy. Maximum adverse drug reactions (ADRs) were reported in Amlodipine mono-therapy group, like ankle oedema, constipation, headache and fatigue.

Discussion and Conclusion: In term of BP control, low-dose combination therapy appears a better therapeutic approach than high-dose mono-therapy.

Keywords: Amlodipine, Hypertension, Low dose combination of telmisartan and amlodipine, Telmisartan

INTRODUCTION

Hypertension is one of the leading public health challenges worldwide. It is common in both developed and developing countries. Reports suggest that the prevalence of hypertension is rapidly increasing in developing countries and is one of the major causes of mortality and morbidity there [1]. The worldwide increasing prevalence of hypertension is attributed mainly to population growth, ageing and behavioural risk factors i.e. unhealthy diet, lack of physical activity, excess weight, harmful use of alcohol and tobacco, and persistent stress.

Essential hypertension is believed to be a result of complex interaction of genetic and environmental factors [2,3]. Increased peripheral resistance is responsible for most of the cases of essential hypertension [4]. Many mechanisms have been suggested to explain rise in peripheral resistance from which the abnormalities of renin-angiotensin system [5] and sympathetic nervous system [6] are most acceptable.

Angiotensin Receptor Blockers (ARB) are first line therapy of Hypertension. Telmisartan is a potent, long-lasting, nonpeptide angiotensin II antagonist that acts on the Angiotensin 1 (AT 1) receptor subtype. The effective dose of Telmisartan is 40–80 mg once daily. Calcium channel blockers (CCBs) are another class of first line anti-hypertensive drugs. Amlodipine, a third generation dihydropyridine calcium antagonist, is illustrated by a lesser negative inotropic effect and higher vascular selectivity compared to other CCBs. The recommended anti-hypertensive dose of Amlodipine in adults is 2.5 to 10 mg. In cases of mild to moderate hypertension, the initiation of drug treatment with a low dose of either CCBs or ARBs is an established therapy. However, optimal treatment strategies in mild to moderate hypertensives who fail to achieve blood pressure (BP) control with low-dose mono-therapy are not well established [7].

This study was planned to compare efficacy and safety of low dose combination of Amlodipine (CCB) and Telmisartan (ARB) vs. high dose mono-therapy of each in mild to moderate hypertensives, who failed to achieve blood pressure control with low dose mono-therapy of either drug.

MATERIALS AND METHODS

This was a prospective, open label, three arms and randomized study. It was conducted in the Out-Patient Department of Medicine, Mahatma Gandhi Hospital, Jaipur, India, in association with Department of Pharmacology, Mahatma Gandhi Medical College, Jaipur, India. Approval from the Institutional Ethics Committee was obtained to conduct the study. The study was also registered at Clinical Trial Registry, India (Reg. No. CTRI/2013/08/003905). A total of 96 adult hypertensive patients, aged 18 to 60 years having uncontrolled blood pressure (systolic BP ≥ 140 to 179 mmHg and/or Diastolic BP ≥ 90 to 109 mmHg) on low dose mono-therapy with either Amlodipine (5mg) or Telmisartan (40 mg) were enrolled in the study after obtaining informed consent in writing. Patients with other concomitant medical conditions, alcohol or drug dependence, pregnant and lactating women and cases of secondary hypertension were not included in the study.

Each enrolled patient was subjected to the detailed medical history, demography and physical examination. Measurements of systolic and diastolic BP were performed manually with a calibrated mercury sphygmomanometer in sitting position. Three

measurements of BP were taken (each 5 minutes apart) and average value was noted. Blood samples were obtained for testing of blood sugar, renal function, liver function and lipid profile.

Patients satisfying inclusion and exclusion criteria were randomized in three treatment groups as following:

- **Group A:** In this group, patients were put on high dose mono-therapy of Telmisartan 80 mg, once daily for eight weeks.
- **Group B:** In this group, patients received high dose mono-therapy of Amlodipine 10 mg, once daily for eight weeks.
- **Group C:** In this group, patients had fixed dose combination of Telmisartan 40 mg and Amlodipine 5 mg, once daily for eight weeks.

Followup visits were performed after two weeks, four weeks and eight weeks. At each visit, complete clinical examination was carried out, including a recording of systolic and diastolic blood pressure (BP). Safety was assessed in terms of both subjective and objective systemic adverse-effects. Subjective symptoms such as headache, dizziness, fatigue, back pain, dyspepsia, myalgia, pruritus and nausea were assessed by questioning the patient at each visit. Objective signs like rash, oedema and hypotension were also obtained. At the end of study i.e. week eight, blood samples were taken for testing blood sugar, renal function, liver function and lipid profile.

RESULTS

A total of 93 subjects were included for analysis; 30 subjects from group A (Telmisartan 80 mg), 32 subjects from group B (Amlodipine 10 mg) and 31 subjects from group C (fixed dose combination of Telmisartan 40 mg and Amlodipine 5mg). Three patients did not complete the study duration and were excluded from statistical analysis. Comparison of blood pressure changes within the group was done by 'ANOVA', comparison of blood pressure changes between various treatment groups was done by 'ANOVA' and 'Post Hoc LSD' and comparisons of adverse drug reactions and effectiveness of eight week treatment on systolic and diastolic BP (characterized by systolic BP ≤ 139 mmHg and diastolic BP ≤ 89 mmHg) in various treatment groups were done by Chi-square test.

Reduction in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) from baseline to end of study visit was statistically highly significant (p-value <0.001) in all treatment groups [Table/Fig-1].

At each study visit, the highest fall in the mean SBP was observed in group C (treated by combination of Telmisartan 40 mg and Amlodipine 5 mg) whereas lowest in group A (treated by Telmisartan 80 mg), and the difference between group A and C was found statistically significant [Table/Fig-2]. Similarly, highest reduction in mean DBP at each study visit was also observed in group C while lowest in group B [Table/Fig-3].

After eight weeks of treatment, SBP target (<139 mm of Hg) was achieved in 80% cases of group A, 90.625% cases of group B and 90.323% cases of group C. But the difference was statistically not significant [Table/Fig-4]. DBP target (< 89 mm of Hg) after eight weeks therapy was attained in 96.667% and 96.774% cases of group A and group C respectively. While group B was placed in bottom as only 68.75% cases achieved DBP target. The difference was found statistically highly significant [Table/Fig-5].

Highest number of patients complaining adverse drug reactions (ADR) were from group B (25%). On the other hand, group C had lowest incidence of ADRs (12.90%) while group A was placed in middle (13.33%). Among various ADRs, fatigue was the most common complaint found in all treatment groups. Total seven cases, two from each group A and C, and three from group B were presented with complaint of fatigue. Nausea and headache were other common complaints which account for total three cases, one from each group. Constipation was found in two cases, both from group B. Dizziness was also complained by two cases, one from group A and B each. One patient presented with ankle oedema from group B [Table/Fig-6].

DISCUSSION

In the present study, low dose combination of Amlodipine 5 mg and Telmisartan 40 mg showed maximum reduction in mean SBP as compared to Telmisartan 80 mg mono-therapy and in mean DBP as compared to Amlodipine 10 mg mono-therapy after two, four & eight weeks treatment. ADRs were also lowest in combination group. Achievement of target SBP and target DBP was also seen in low dose combination group as compared to Amlodipine or Telmisartan alone.

A study in Japan reported that low dose combination of Telmisartan 40 mg and Amlodipine 5 mg significantly reduced 24h mean and clinical BP in patients whose hypertension was not controlled by 5 mg of Amlodipine [8]. In another study, the addition of Telmisartan 40 mg to Amlodipine 5 mg produced statistically significant reductions in trough seated DBP than Amlodipine 5 mg alone [9]. The Telmisartan–Amlodipine clinical development program included a pivotal eight weeks, randomized, double-blind, placebo-controlled clinical trial to demonstrate the additive nature of combination of Telmisartan and Amlodipine across a wide range of doses. In this study, combination of Telmisartan and Amlodipine significantly lowered the SBP and DBP compared to mono-therapies [10]. Clinical studies suggest that combination drug therapy also results in more rapid BP control in addition to the more patients achieving BP target [11]. Since blood pressure is result of several physiological mechanisms, thus an attempt to block one (as in mono-therapy) tends to increase compensatory activity of others. Therefore, two drugs from different classes with complimentary mechanisms of action may result in additional BP control compared with either agent used alone. To attain

Follow up visit	Group A (n 30)		Group B (n 32)		Group C (n 31)	
	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Baseline	153.8±8.31	93.2±6.048	154.1±8.553	94.19±6.631	153.5±10.29	94±5.441
Week 2	143.8±7.151	85.27±5. 078	142.3±7.789	87.94±6.211	140.2±9.039	83.16±5.508
Week 4	135.8±6.133	79.27±5.521	133.8±6.154	84.31±6.347	130.3±7.741	78.19±5.375
Week 8	132±7.575***	77.2±5.397***	129.7±7.293***	83.44±7.89***	126.4±9.2***	76.32±5.659***

[Table/Fig-1]: Effect of treatment on mean SBP and DBP in various treatment groups. (***p<0.001, highly significant)

Follow up Time	Change in SBP (mmHg) Group A (n 30)	Change in SBP (mmHg) Group B (n 32)	Change in SBP (mmHg) Group C (n 31)	Significant Difference Among Groups
Week 0 to 2	10.00±2.877	11.75±2.862	13.29±4.577	A-C
Week 2 to 4	18.00±4.756	20.31±5.233	23.23±6.190	A-C
Week 4 to 8	21.80±5.592	24.38±6.333	27.10±7.134	A-C

[Table/Fig-2]: Changes in mean SBP in follow up in various treatment groups

Follow up Time	Change in DBP (mmHg) Group A (N 30)	Change in DBP (mmHg) Group B (N 32)	Change in DBP (mmHg) Group C (N 31)	Significant Difference Among Groups
Week 0 to 2	7.93±2.900	6.25±3.203	10.84±3.532	A-B, A-C, B-C
Week 2 to 4	13.93±4.118	9.88±4.125	15.81±6.008	A-B, B-C
Week 4 to 8	16.00±5.965	10.75±5.099	17.68±6.534	A-B, B-C

[Table/Fig-3]: Changes in mean DBP in follow up in various treatment groups

Status of SBP after 8 week treatment	Group A	Group B	Group C	Grand Total
Remained Hypertensive after 8 week treatment (≥ 140 mm of Hg)	6 (20.00)	3 (9.375)	3 (9.677)	12 (12.903)
Became Normotensive after 8 week treatment (≤ 139 mm of Hg)	24 (80.00)	29 (90.625)	28 (90.323)	81 (87.097)
Grand Total	30 (100.00)	32 (100.00)	31 (100.00)	93 (100.00)

[Table/Fig-4]: Distribution of cases according to effectiveness of 8 week treatment for SBP in various treatment groups

Status of DBP after 8 week treatment	Group A	Group B	Group C	Grand Total
Remained Hypertensive after 8 week treatment (≥ 90 mm of Hg)	1 (3.333)	10 (31.25)	1 (3.226)	12 (12.90)
Became Normotensive after 8 week treatment (≤ 89 mm of Hg)	29 (96.667)	22 (68.75)	30 (96.774)	81 (87.10)
Grand Total	30 (100.00)	32 (100.00)	31 (100.00)	93 (100.00)

[Table/Fig-5]: Distribution of cases according to effectiveness of 8 week treatment for DBP in various treatment groups

Various types of ADRs	Group A	Group B	Group C	Grand Total
Fatigue	2	3	2	7
Nausea	1	1	1	3
Headache	1	1	1	3
Constipation	0	2	0	2
Dizziness	1	1	0	2
Ankle Oedema	0	1	0	1
Grand Total	**5**	**9**	**4**	**18**

[Table/Fig-6]: Distribution of ADRs in various treatment groups (N=18)

the specified BP goals and to reduce cardiovascular morbidity and mortality, the majority of patients with hypertension require combination of two or more antihypertensive drugs [7,12]. In a meta-analysis, five times more effective BP control was observed with combination of drugs from different antihypertensive classes than increasing the dose of one drug [13]. Hypertensive patients who failed to achieve BP target by anti-hypertensive mono-therapy may therefore benefit by adding another agent from a different class of antihypertensive drug.

In our study, 25% patients from Amlodipine 10 mg mono-therapy group reported ADRs like ankle oedema, constipation, headache and fatigue. All ADRs were of mild nature and did not require discontinuation of therapy. In an eight weeks factorial study, 37.3% patients reported at least one adverse event. In that study headache and peripheral oedema were the most commonly reported adverse events. Though, headache was more frequently reported in the placebo group. Peripheral oedema was highest reported in the Amlodipine 10 mg group however the incidence was comparatively lower when Amlodipine was used with Telmisartan [10]. In another study on anti-hypertensive drugs, oedema was most commonly reported ADR, and was mainly seen in Amlodipine group [9,13]. Moreover, such approach of combining a renin-angiotensin system (RAS) inhibitor to a Calcium channel blocker appears to be associated with low incidence of CCB-related oedema [14]. This attenuation of oedema appears to be due to the ability of RAS blockers to counteract with CCBs induced microcirculatory changes. Though, the exact mechanism remains to be established [15].

The dose of anti-hypertensive agent is often increased if initial mono-therapy does not produce the desired BP-lowering effect. Up-titrating anti-hypertensive dose may improve BP response rates but usually also increase the occurrence of side effects which, in turn, may lead to reduced patient compliance and sometimes even treatment discontinuation.

This study indicates that clinicians can be assured of efficacy and safety of low dose combination than monotherapy. Promoting evidence based medicine for clinical decision making, physicians should rely on how the agents perform when administered together in add-on studies and how each component performs as monotherapy in reducing BP, achieving BP goals and reducing outcomes, as well as considering patient factors such as response to and tolerance of such agents as monotherapy and cost. The availability of effective and well tolerated fixed-dose combination antihypertensive agents should encourage primary-care physicians to be more willing to use such therapies in a timely manner when BP goals are not being achieved with monotherapy. This approach would improve BP control rates in the US and worldwide [16].

CONCLUSION

In this study, a low dose Telmisartan–Amlodipine combination has demonstrated significantly greater BP reductions for both SBP and DBP compared to high dose mono-therapy of Telmisartan and Amlodipine in the overall study population. This combination is well tolerated with a safety profile consistent with its mono-therapy components. So, in terms of BP control, low-dose combination therapy appears a better therapeutic approach than high-dose mono-therapy for mild to moderate hypertensive patients who failed to achieve BP target on low-dose mono-therapy.

LIMITATIONS & RECOMMENDATIONS

One limitation was the small duration of our study. It is recommended that further studies should be done for a longer duration to assess the efficacy and safety of low dose combination over high dose monotherapy in mild to moderate hypertensive patients who failed to achieve BP target on low-dose mono-therapy. There is a paucity of data comparing different fixed-dose combinations; and very few studies have investigated the impact of fixed-dose combinations on achievement of BP goals, including both systolic BP and diastolic BP. So, another recommendation is to compare different low dose combinations in terms of efficacy and safety to bring a paradigm shift in the way, mild to moderate hypertension is treated.

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