A COMPARATIVE STUDY TO EVALUATE TOLERABILITY AND EFFICACY OF TWO FIXED DOSE-COMBINATIONS OF AMLODIPINE/TELMISARTAN VERSUS AMLODIPINE/HYDROCHLOROTHIAZIDE IN STAGE II HYPERTENSION.

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ABSTRACT

The aim of this study was to evaluate the efficacy and tolerability of fixed dose combination (FDC) of Amlodipine (5mg) + Telmisartan (40mg) compared with FDC of Amlodipine (5mg) + Hydrochlorothiazide (12.5mg) in Indian patients with stage II hypertension. Patients between the age group 18 to 65 years with stage II hypertension were treated with oral FDC of A + T or FDC of A + HCTZ once a day before breakfast for 8 weeks. Primary efficacy end point was reduction in systolic BP/ diastolic BP and number of responders (SBP/DBP <130/<80 mmHg). Tolerability was assessed by comparing the incidence of adverse events. The percentage reduction in SBP in A + T group was 23.1% as compared to 14.94% in A + HCTZ group. Similarly the percentage reduction in DBP in A + T group was 14.68% as compared to 8.3% in A + HCTZ group. From the result obtained FDC of A + T seems to be significantly more effective in controlling blood pressure as compared to FDC of A + HCTZ. 12/60 patients in A + T group achieved target SBP <130 mmHg. The prevalence of adverse events was similar in both treatment groups. All AEs were mild to moderate in severity and did not require any rescue medication. Although the occurrence of peripheral edema was more in A + HCTZ group (30 %) as compared to A + T group (10 %). Both the treatment regimens were well tolerated.

Key Words: Amlodipine, Telmisartan, Hydrochlorothiazide, Stage II hypertension.

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INTRODUCTION
High blood pressure (BP) is a leading risk factor for cardiovascular morbidity and mortality[^1]. Effective antihypertensive therapy is available, but recognition and proper management of hypertension and BP goal achievement are still poor. Furthermore, recent (2012) studies show that for every known person with hypertension there are two persons with either undiagnosed hypertension or prehypertension[^2].

High blood pressure (BP) is a major public health problem in India and its prevalence is rapidly increasing among both urban and rural populations. In fact, hypertension is the most prevalent chronic disease in India[^3][^4]. The prevalence of hypertension ranges from 20-40% in urban adults and 12-17% among rural adults. The number of people with hypertension is projected to increase from 118 million in 2000 to 214 million in 2025, with nearly equal numbers of men and women[^5]. A survey of 26,000 adults in south India showed a hypertension prevalence of 20% (men 23% and women 17%) but 67% of those with hypertension were unaware of their diagnosis. Majority of hypertensive subjects still remain undetected and the control of hypertension is also inadequate. This calls for urgent prevention and control measures for hypertension[^6].

Achievement of BP goals is associated with significant benefits in cardiovascular morbidity and mortality[^1]. Although evidence suggests these goals are attainable, only about one third of patients are successful in meeting them[^7]. Clinical trials in hypertension suggest that single drug therapy may not achieve the target BP goals and related reductions in cardiovascular morbidity and mortality[^8][^9].

An angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ARB) may be recommended as first-line treatment and adding a diuretic or calcium channel blocker (CCB) to it is much more likely to result in achievement of the BP goal. Furthermore, since hypertension has been associated with target organ damage, lowering the BP has the additional advantage of improving morbidity and mortality and, if intervention is initiated early enough, preventing organ damage[^10]. Thus, attaining BP goal is crucial in the treatment of hypertension. CCBs are a chemically heterogeneous group of substances that effectively reduce elevated BP in all age groups and have been found to have organoprotective properties.
Amlodipine, a peripheral arterial vasodilator, inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle and acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and BP. The ARB telmisartan has been approved by the US Food and Drug Administration for the treatment of hypertension.\textsuperscript{[11]}

Telmisartan has a long half-life (~24 hours) and duration of action. Significantly greater mean changes in SBP and diastolic BP (DBP) were seen with telmisartan 40 mg (–14.21/–8.61) and 80 mg (–15.0/–9.71) during the 24-hour dosing period and during the last 6 hours (–10.7/–6.8 and –12.2/–7.1, respectively) before dosing compared with losartan 50 mg (–10.3/–6.0 and –6.0/–3.7) (all, P < 0.05).

Low-dose thiazide-type diuretics are recommended as initial therapy for most hypertensive patients. Hydrochlorothiazide with other drug combination shows better reduction in blood pressure than single mono therapy.

Telmisartan 40 mg and 80 mg has shown significantly greater mean changes in SBP and DBP as compared to Losartan 50 mg.

FDC of T + A have shown significantly reduction in SBP and DBP as compared to monotherapy of A. The prevalence of adverse events were not significantly difference between two treatment groups.\textsuperscript{[12]}

The efficacy and safety of FDC of A plus Amiloride/ HCTZ has previously been compared with FDC of A + T in Hypertensive patients. Both combination regimen were effective and safe for the high-risk hypertensive patients.\textsuperscript{[13]}

The aim of the presence study was to evaluate the Tolerability and Efficacy of Two Fixed Dose-Combinations of Amlodipine/Telmisartan versus Amlodipine/Hydrochlorothiazide in Stage II Hypertensive patients.

**METHOD**

The present study was comparative, 8 week single centric, prospective, randomized study was conducted in Indian patients. Study protocol was reviewed and approved by the review boards of the participating institutions. Follow-up visits were carried out at 2, 4, and 8 weeks of treatment.
**Inclusion and exclusion Criteria**

Indian male and female patients aged 18 to 65 years with established stage II uncomplicated essential hypertension (SBP, 160–179 mm Hg; DBP, 100–109 mm Hg) and those not responding to monotherapy to ARB, CCB, or Thiazide Diuretics were eligible for participation in the study. Patients hypersensitive to ARB, CCB, thiazide Diuretics or who were pregnant or breastfeeding were excluded from the study.

Additional reasons for exclusion included severe hypertension, malignant hypertension, or secondary hypertension; history of acute myocardial infarction; coronary revascularization; unstable angina pectoris; arrhythmia requiring treatment during the previous 6 months; New York Heart Association class IV heart failure or severe aortic or mitral valvular disease requiring medical treatment or causing hemodynamically significant disturbances; stroke or transient ischemic attack within the previous 6 months; significant cardiac, hepatic, renal, or cerebrovascular disease; uncontrolled diabetes mellitus; and/or other serious illness (eg, malignancy, HIV). Patients with concurrent use of other hypertensive, including diuretics, α-blockers, β-blockers, or CCBs, and those with malignancy, severe chronic systemic diseases, or any condition likely to hamper compliance with the study protocol (eg, remote location, inability to follow study instructions)

All eligible patients were provided an oral explanation about the nature of the study and about the study drugs by the investigator. An information sheet was provided in a language understood by the patient, and written informed consent was obtained from each participant prior to patient enrollment.

Enrolled patients were receive an oral tablet formulation of an FDC of amlodipine 5 mg + telmisartan 40 mg (A + T) or amlodipine 5 mg + Hydrochlorothiazide 12.5 mg (A + HCTZ), once daily before breakfast for 8 weeks.

The use of any other antihypertensive treatment (other than the exercise and dietary modifications) was not permitted during the study period. However, the use of medications for concomitant conditions (eg, antidiabetic agents, acetylsalicylic acid) and any other treatments (eg, multivitamins, antioxidants, and mineral supplements) that would not interfere with the study drugs was permitted.
After at the end of the study, treatment with either study drug and/or any other antihypertensive agent at an appropriate dose was continued at the discretion of the attending physician.

**Efficacy measurement**

The primary efficacy end points were reductions in clinical SBP and DBP from baseline (week 0) of study end (week 8) and the number of *responders* (those who achieved clinical SBP/DBP of <130/<80 mm Hg respectively).

At each visit, BP was measured in the morning using a standard 6-inch cuff mercury sphygmomanometer that was calibrated prior to use. Patients were sitting upright in a chair with their feet on the floor and 1 arm supported at heart level. Sitting BP was measured 2 times with an interval of ~5 minutes, and the mean of the 2 measurements was calculated. Elevated BP was confirmed by measuring the BP in the other arm (mean of 2 measurements).

**Tolerability assessment:** At the screening visit each patient underwent a physical examination and medical history, including measurements of SBP, DBP and demographic data were recorded. Follow-up visits were carried out at 2, 4, and 8 weeks of treatment and included BP measurements. Peripheral edema was identified on physical examination. At each visit, AEs were also collected using patient questioning, and investigator observation and were recorded on case-report forms.

**Statistical Analysis:** Data of all randomized patients who received all doses of study medications and completed the study were included. Data were expressed as mean ± SD. Difference in SBP/DBP were analyzed using paired and unpaired t test, whereas response rate and AE profile in each group were represented in percentage. Data analysis were performed using Graphpad prism 6.0 software. Differences were considered statistically significant at *P* ≤ 0.05.

**RESULTS**

- **Patient enrollment and disposition:** A total of 60 patients (41 male, 19 female) who met all the inclusion criteria and none of the exclusion criteria were enrolled in the study (n = 30 for A + T, n = 30 for A+HCTZ). No patient was lost to follow up. Thus data of all 60 patients was included in statistical analysis.
• Demographic Data

As shown in the table 1, demographic data of enrolled patients was collected.

Table 1 Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>A + T (Group I) n = 30</th>
<th>A + HCTZ (Group II) n = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>46.25 ± 7.39</td>
<td>45.33 ± 8.51</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.47 ± 10.93</td>
<td>158.17 ± 7.49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.93 ± 10.59</td>
<td>62.17 ± 12.56</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.14 ± 5.32</td>
<td>25.09 ± 5.83</td>
</tr>
</tbody>
</table>

A + T = Amlodipine + Telmisartan
A + HCTZ = Amlodipine + Hydrochlorothiazide
BMI = Body Mass Index

Change in Blood Pressure: As shown in the table 2 and figure 1, treatment with A + T as well as with A + HCTZ shows a significant decrease (P< 0.0001) in SBP and DBP after 2, 4 and 8 weeks of treatment as compared to baseline. A significant difference (P< 0.0001) in decrease in SBP and DBP was observed between the groups at week 4 and week 8 of treatment.

Table 2 Change in Blood pressure after treatment

<table>
<thead>
<tr>
<th></th>
<th>A + T</th>
<th>A + HCTZ</th>
<th>A + T</th>
<th>A + HCTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>0 Week</td>
<td>169.87 ± 5.72</td>
<td>103.93 ± 3.07</td>
<td>154.57 ± 5.90</td>
<td>97.50 ± 3.04</td>
</tr>
<tr>
<td>2 Week</td>
<td>154.57* ± 5.90</td>
<td>97.50* ± 3.04</td>
<td>141.9*# ± 5.88</td>
<td>92.1*# ± 3.20</td>
</tr>
<tr>
<td>4 Week</td>
<td>141.9*# ± 5.88</td>
<td>92.1*# ± 3.20</td>
<td>144.4*# ± 6.08</td>
<td>88.67*# ± 3.26</td>
</tr>
<tr>
<td>8 Week</td>
<td>130.63*# ± 6.08</td>
<td>88.67*# ± 3.26</td>
<td>144.4*# ± 5.77</td>
<td>88.67*# ± 5.77</td>
</tr>
</tbody>
</table>

* P < 0.0001 versus baseline.
#P < 0.0001 between groups.

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure
Notes: A + T = Amlodipine + Telmisartan, A + HCTZ = Amlodipine + Hydrochlorothiazide

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure

**Reduction in Blood Pressure:** As shown in figure 2, mean reduction in SBP at week 4 in A + T group was 27.99 mmHg (16.46 %) as compared to 21.17 mmHg (12.47 %) in A + HCTZ group. The mean reduction in DBP at week 4 in A + T group was 11.83 mmHg (11.38 %) as compared to 7.17 mmHg (6.89 %) in A + HCTZ group. The mean reduction in SBP at week 8 in A + T group was 39.23 mmHg (23.1 %) as compared to 25.36 mmHg (14.94 %) in A + HCTZ group. The mean reduction in DBP at week 8 in A + T group was 15.26 mmHg (14.68 %) as compared to 8.63 mmHg (8.3 %) in A + HCTZ group. These results indicate that treatment with A + T shows a better reduction in mean blood pressure (SBP/DBP) and percentage reduction in BP as compared to treatment with A + HCTZ at week 4 and week 8 of treatment.

**Figure 1 Change in Blood Pressure after treatment**

**Figure 2 Reduction in blood pressure**
Tolerability Assessment: As shown in table 4, A total of 7/30 patients (23.33%) in the A + T group experienced AEs compared with 9/30 Patients (30%) in the A + HCTZ group. All AEs were mild to moderate in severity and did not require use of any rescue medication. The most common AEs in A + T group were peripheral edema (3/30 patients, 10%), headache (2/30 patients, 6.67%), cough (1/30 patients, 3.34%), dizziness (1/10 patients, 3.34 %). The most common AEs in A + HCTZ group was peripheral edema (9/30 patients, 30%).

Table 4 Adverse Events

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>ADR</th>
<th>A + T n (%)</th>
<th>A + HCTZ n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peripheral edema</td>
<td>3 (10)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>2</td>
<td>Headache</td>
<td>2 (6.67)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cough</td>
<td>1 (3.34)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Dizziness</td>
<td>1 (3.34)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>7 (23.33)</td>
<td>9 (30)</td>
</tr>
</tbody>
</table>

A + T = Amlodipine + Telmisartan
A + HCTZ = Amlodipine + Hydrochlorothiazide
ADR = Adverse Drug Reaction

Responders: Out of total enrolled patients (n=60), 12 patient achieved target SBP (<130 mmHg). Although treatment with both A +T and A + HCTZ resulted in a significant fall in SBP and DBP at week 8, none of the patients achieved the target blood pressure of <130/ <80 mm Hg.

DISCUSSION

Blood pressure level <130/<80 mmHg is recommended in hypertensive patients as it provides additional benefit with regard to target organ protection (morbidity) and cardiovascular mortality. [14]

Antihypertensive that play an important role for morbidity and mortality are CCB, ARB and thiazide diuretic. These drugs have favorable metabolic profile. [15]

The results of the present study indicate the antihypertensive efficacy of A + T and A + HCTZ. However treatment with A (40mg) + T (5mg) was found to be significantly more efficacious in reducing BP at the end of 8 week as compared to A (40mg) + HCTZ (12.5 mg) treatment.

The reduction in SBP and DBP was significantly greater in patients treated with A + T as compared to A + HCTZ (23.1 %, 14.94 % and 14.68 %, 8.3 % respectively) p< 0.0001.
After treatment with A + T, the percentage reduction in SBP and DBP at 8 week [23.1 %, 14.68 % respectively] in our study is similar to that seen in the study of Sharma et al. in which they compared the FDC A + T with Amlodipine. The percentage reduction in SBP and DBP at 8 week [22.80 % and 16.84 % respectively] with A + T was significantly more as compared to Amlodipine monotherapy in their study.

After treatment with A + HCTZ, the percentage reduction in SBP and DBP at 8 week [14.94 % and 8.3 % respectively] in our study is similar to the results of Destro et al. in which they compared the triple combination therapy of amlodipine, valsartan and hydrochlorothiazide with dual combination of Amlodipine and Hydrochlorothiazide. [16] The percentage reduction in SBP and DBP at 8 week [13.80 % and 7.90 % respectively] was observed in A + HCTZ group in their study.

In our study the incidence of peripheral edema (3/30 patients, 10%) was less in A + T group as compared to A + HCTZ (9/30 patients, 30 %) which is almost similar to the results of Sharma et al in which peripheral edema was reported in 9/106 patients (8.5 %) in the A + T group. The incidence of peripheral edema in A + HCTZ group as reported by Destroy et al was 37/208 patients (17.8 %).

Antihypertensive medication should also have good tolerability profile in addition to reducing BP and maintaining it at controlled levels because severe AEs may decrease patient compliance leading to discontinuation of treatment. [17] The most common AEs in the present study with FDC A + T and FDC A + HCTZ were peripheral edema. However this study was not powered to detect the difference in the incidence of peripheral edema. The incidence of peripheral edema was found to be numerically lower in A + T group as compared to A + HCTZ group.

Amlodipine is a CCB that induces edema caused by the increased the capillary hydrostatic pressure that result from the greater dilation of pre capillary than the post capillary vessel. Edema that is caused by the CCB does not appear to be related to fluid retention but due to an increase in capillary pressure leading to leakage of fluid.
Adding HCTZ thiazide diuretic may have little or no effect on CCB induced edema because diuretics act only by reducing water retention and do not affect vasodilatory induced fluid pooling. [18]

Here the dose of HCTZ given in the second group is 12.5 mg. So, further studies are required to investigate whether increasing the dose of HCTZ has a better effect in reducing CCB induced edema. Addition to CCB with ARB or ACE inhibitor has greater control in reduction of peripheral edema. However ACE inhibitor have cough as a major adverse effect. It is preferable to use ARB in addition to CCB.

The response rate is low in this study. Only some of the patients (12/30) achieved SBP goal <130 mmHg in A + T group. Multicentric studies with larger patient pool and longer duration of follow up (up to 12 weeks or more) may be required for a better comparison of efficacy and safety of both these combinations.

CONCLUSION
In stage II hypertensive patients the FDC of A + T seems to be significantly more effective in controlling blood pressure as compared to FDC of A + HCTZ. Both the treatment regimens were well tolerated.

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