A COMPARATIVE STUDY TO EVALUATE THE EFFECTS OF ANGIOTENSIN RECEPTOR BLOCKER AND CALCIUM CHANNEL BLOCKER COMBINATIONS ON RENAL FUNCTION AND LIPID PROFILE IN HYPERTENSIVE PATIENTS

Vinty Mary Johnson*1, Allen George1, Susmin Eapen1, Jeenu Joseph2, Dr. Sajan Ahmad Z MD, DM, DNB3 and Dr. Santhosh M. Mathews4

1Department of Pharmacy Practice, Pushpagiri College of Pharmacy, Thiruvalla.
2Department of Pharmacognosy, Pushpagiri College of Pharmacy, Thiruvalla.
3Assistant Professor, Department of Cardiology, Pushpagiri Medical College Hospital, Thiruvalla.
4Principal, Pushpagiri College of Pharmacy, Thiruvalla.

ABSTRACT

Background: Hypertension is the most common cardiovascular disease and is associated with metabolic abnormalities like lipid profile rearrangement. It may also damage kidney. Antihypertensive drugs have an organ protective effect thereby it prevents cardiovascular complications. Angiotensin receptor blocker-Calcium channel blocker combinations are one of the important therapy used in hypertensive patients. The effect of this combination on renal function, lipid profile and potassium was not well documented in most of the studies. So the study of this effect was undertaken in this study. Method: This prospective observational study selected 72 patients of greater than 18 years of age based on inclusion criteria and excluded patient taking other drugs that affect our study parameters. 47 patients in this study were males and 25 were females. This 6 month study included a 3 month followup. Patient taking Telmisartan Cilnidipine combination and Telmisartan amlodipine combination were selected. Renal parameters like Creatinine, eGFR and potassium and lipid parameters like LDL, HDL, TGL, total cholesterol were noted before taking this combination and after 3 months of taking this combination. Results: This study showed that Telmisartan and Cilnidipine significantly (p=0.06, p<0.10) reduced triglyceride than Telmisartan and Amlodipine combination. On renal parameters, Telmisartan and
Cilnidipine combination significantly (p=0.07885, p<0.10) increased eGFR than Telmisartan and amlodipine combination. Both combinations reduced Creatinine but on comparison this reduction was not significant (p=0.8108, p<0.10). Total cholesterol, HDL, LDL and potassium did not show any significant change after 3 months. **Conclusion:** This study showed that Telmisartan Cilnidipine combination is more effective than Telmisartan amlodipine combination.

**KEYWORDS:** Calcium channel blocker, Angiotensin receptor blocker, Estimated glomerular filtration rate, Telmisartan and Cilnidipine, Telmisartan and amlodipine.

**INTRODUCTION**

Hypertension is a condition of persistently elevated arterial blood pressure. Hypertension is often called "the silent killer" because it generally has no symptoms until serious complications develop. Usually a mean arterial pressure greater than 110mm Hg under resting conditions is considered to be hypertensive; this level normally occurs when the diastolic blood pressure is greater than 90 mm Hg and the systolic pressure is greater than about 135-140 mm Hg.

**Calcium Channel Blocker**

- JNC-8 guidelines recommend CCBs as the first line drugs for the treatment of hypertension. Out of various subtypes, CCBs mainly act on L-type, T-type and N-type calcium channels.\(^2\)
- The dihydropyridines that act on L-type calcium channels in the peripheral arterioles reduce the blood pressure by reducing total peripheral resistance.\(^3\)
- Cilnidipine has an inhibitory action on the sympathetic N-type Ca\(^{2+}\) channels along with L-type Ca\(^{2+}\) channels; because of this action, Cilnidipine is a unique calcium channel blocker. In many animal and clinical trials, it’s cardioprotective, renoprotective and neuroprotective effects are shown. Cilnidipine is a fourth-generation calcium channel blocker.\(^4\)
- Amlodipine is a third generation dihydropyridine calcium channel blocker. It inhibit ca\(^{2+}\) influx into vascular smooth muscle cells and myocardial cells which result in decreased peripheral vascular resistance.\(^5\)
Angiotensin Receptor Blocker

ARBs include

Telmisartan, Losartan, Olmesartan, Eprosartan, Valsartan, Olmesartan, Azilsartan

ARBs act by blocking the binding of angiotensin II on AT1receptors which are present on blood vessels and other tissues. Infrequent ADRs associated with therapy include: first dose orthostatic hypotension, rash, diarrhea, dyspepsia, abnormal liver function, muscle cramp, myalgia, back pain, insomnia, decreased haemoglobin levels, renal impairment, pharyngitis, hyperkalemia and/or nasal congestion. Telmisartan is a PPARα agonist and a selective PPARγ modulator.

Estimating Glomerular Filtration Rate

The estimate of glomerular filtration rate based on serum Creatinine concentration is a widely used method, eventhough serum Creatinine concentration fluctuate with disease state and patient conditions.

MDRD equation

GFR rate can be calculated by MDRD equation

\[
GFR (\text{mL/min}/1.73 \text{ m}^2) = 175 \times (\text{S}_{\text{cr}})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black}).
\]

Where eGFR- estimated GFR.

This method does not require height and weight because the results reported normalized to 1.73m² body surface area. It estimates GFR adjusted for body surface area.

Morisky medication adherence scale (MMAS-8)

WHO defines adherence as “the extent to which the patient follows medical instructions”. Morisky medication adherence scale is a tool is used measure non adherence. It is also known as morisky scale. It’s a valuable resource to address concerns such as forgetting to take medications. It consist of 8 questions. These questions are geared in such a way to avoid “yes-saying” bias commonly seen with chronic care patients. By analysing how the patient scored on the scale, clinicians can identify underlying issues that prevent patients from taking their medication correctly.

MATERIALS AND METHOD

This prospective observational study was conducted in the department of cardiology at Pushpagiri Medical College Hospital to identify which Calcium channel blocker (Amlodipine/Cilnidipine) is more effective with Angiotensin receptor blocker (Telmisartan)
on renal function and lipid profile in hypertensive patients. 72 patients were selected (36 patients on Telmisartan amlodipine combination and 36 on Telmisartan Cilnidipine combination) and the selection of these patients were based on the inclusion and exclusion criteria. This 6 month study included a 3 month followup. Majority of patients in this study were found to belong to 51-60 and followed by 71-80 years. 47 patients in this study were males and 25 were females. Out of 72 patients, 38 cases had type 2 DM.

**Inclusion Criteria**
- Patients equal to or above 18 years.
- Both male and female patients receiving ARB-CCB combinations.
- Those who give consent to participate in the study.

**Exclusion Criteria**
- Patient who are not willing to give consent.
- Patient taking drugs like lithium, potassium sparing diuretics, statins.
- Pregnancy
- Lactation
- Patients taking other drugs having significant effect on kidney and lipid profile.
- Chronic kidney disease.

**Data Collection**
Predesigned data collection form was used for recording the patient complaints, laboratory parameters. This study was conducted after getting approval from institution ethical committee (no-PCP/E1/01A/05/2019). Patient taking other drugs that affecting study parameters were excluded. Medication adherence was assessed by using MMAS-8 questionnaire. Information on lipid parameters like total cholesterol, HDL, LDL, TGL and renal parameters like eGFR and serum creatinine and also serum potassium at baseline prior to starting Telmisartan+Amlodipine or Telmisartan+Cilnidipine and at the end of 3 months of therapy were collected. Combinations selected –Tazloc AM, Cilacar T, Cresar AM, Eritel LN. Dose –Telmisartan 40 mg, Cilnidipine 10mg, Amlodipine -10 mg. Estimated glomerular filtration rate was calculated using MDRD equation. Using Morisky medication adherence questionnaire, medication adherence was assessed.

**Scores in MMAS-8 scale**
>2=low adherence
1-2=medium adherence
0=high adherence

Statistical analysis
By analyzing the changes in these parameters, the effectiveness was assessed. Chi square test was used for the statistical analysis of the data. Significance level was selected based on the p<0.10.

RESULTS
Table no. 1: Distribution of patients according to age.

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upto 40</td>
<td>5</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>6</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>24</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>16</td>
<td>22%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>71-80</td>
<td>17</td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above 80</td>
<td>4</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1: Distribution of patients according to age.

In this study majority of patients belong to 51-60 years of age.

Table 2: Comparison of Total cholesterol Telmisartan +Amlodipine and Telmisartan+Cilnidipine taking patients on consultation and after 3 months.

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan+Amlodipine</th>
<th>Chisquare</th>
<th>Degree of freedom</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>176mg/dl</td>
<td>161mg/dl</td>
<td>0.000047</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Follow up</td>
<td>176mg/dl</td>
<td>161mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 2: Comparison of Total cholesterol Telmisartan + Amlodipine and Telmisartan+Cilnidipine taking patients on consultation and after 3 month.

The total cholesterol level not changed after 3 months. The p-value is 1. So the result is not significant at p˂ 0.10.

Table 3: Comparison of triglyceride in Telmisartan + Amlodipine and Telmisartan + Cilnidipine taking patients on consultation and after 3 months.

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan+ Amlodipine</th>
<th>Chisquare</th>
<th>D f</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>156mg/dl</td>
<td>158mg/dl</td>
<td>3.415</td>
<td>1</td>
<td>0.064</td>
</tr>
<tr>
<td>Followup</td>
<td>106mg/dl</td>
<td>147mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3: Comparison of triglyceride in Telmisartan +Amlodipine and Telmisartan + Cilnidipine taking patients on consultation and after 3 months.
The p value is 0.064. This result is significant at p < 0.10. In Telmisartan + Cilnidipine group serum triglyceride reduced significantly.

**Table 4: Comparison of HDL in Telmisartan + Amlodipine and Telmisartan + Cilnidipine taking patients on consultation and after 3 months.**

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan + amlodipine</th>
<th>Chisquare</th>
<th>Df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>45.69 mg/dl</td>
<td>49.44 mg/dl</td>
<td>0.00183</td>
<td>1</td>
<td>0.989</td>
</tr>
<tr>
<td>Followup</td>
<td>45.7 mg/dl</td>
<td>49.3 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Fig. 4: Comparison of HDL in Telmisartan + Amlodipine and Telmisartan + Cilnidipine taking patients on consultation and after 3 months.](image)

In Telmisartan + Cilnidipine and Telmisartan + Amlodipine group, HDL level is not changed after 3 months of therapy. The p value is 0.989. So this result is not significant at p < 0.10.

**Table 5: Comparison of LDL in Telmisartan + Amlodipine and Telmisartan + Cilnidipine taking patients on consultation and after 3 months.**

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan + amlodipine</th>
<th>Chisquare</th>
<th>Df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>93.3 mg/dl</td>
<td>94.9 mg/dl</td>
<td>0.0001104</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Followup</td>
<td>93.2 mg/dl</td>
<td>95 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 5: Comparison of LDL in Telmisartan +amlodipine and Telmisartan +Cilnidipine taking patients on consultation and after 3 months.

In Telmisartan +Cilnidipine and Telmisartan +amlodipine group the LDL level not changed much after 3 month of therapy. The $p$-value is 1. So this result is not significant at $p < 0.10$.

Table 6: Comparison of creatinine in Telmisartan +amlodipine and Telmisartan +Cilnidipine taking patients on consultation and after 3 months.

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan+ amlodipine</th>
<th>Chisquare</th>
<th>Df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>1.758mg/dl</td>
<td>1.008mg/dl</td>
<td>0.0573249</td>
<td>1</td>
<td>0.8108</td>
</tr>
<tr>
<td>Followup</td>
<td>1.144mg/dl</td>
<td>1.02mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6: Comparison of creatinine in Telmisartan +amlodipine and Telmisartan +Cilnidipine taking patients on consultation and after 3 months.
On followup, in Telmisartan +Cilnidipine group serum Creatinine level was reduced from the initial value than Telmisartan +amlodipine group. But this result is not significant at p < 0.10.

Table 7: Comparison of eGFR in telmisartan+amlodipine and telmisartan +cilnidipine taking patients on consultation and after 3 months.

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan+amlodipine</th>
<th>Chisquare</th>
<th>Df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>38.08ml/min/m²</td>
<td>80.33ml/min/m²</td>
<td>3.08846</td>
<td>1</td>
<td>0.07885</td>
</tr>
<tr>
<td>Followup</td>
<td>62.39ml/min/m²</td>
<td>83.7ml/min/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 7.

On followup, eGFR increased to a greater extent from the initial level for Telmisartan +Cilnidipine group compared to Telmisartan +Amlodipine group. The p-value is 0.07885. So the result is significant at p <0.10

Table 8: Comparison of potassium in telmisartan+amlodipine and telmisartan +cilnidipine taking patients on consultation and after 3 months.

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan+amlodipine</th>
<th>Chisquare</th>
<th>Df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>4.14mEq/l</td>
<td>4.05mEq/l</td>
<td>0.00001191</td>
<td>0.9972</td>
<td></td>
</tr>
<tr>
<td>Followup</td>
<td>4.34mEq/l</td>
<td>4.26mEq/l</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
On followup, serum potassium level in both Telmisartan +Cilnidipine and Telmisartan +Amlodipine group increased from initial value. The p-value is 0.997. So the difference is not significant at p< 0.10.

**Distribution of patient according to medication adherence.**

**Table no. 9.**

<table>
<thead>
<tr>
<th></th>
<th>Cilnidipine + telmisartan</th>
<th>Telmisartan +amlodipine</th>
<th>Chisquare</th>
<th>Df</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium adherence</strong></td>
<td>28</td>
<td>27</td>
<td>0.077</td>
<td>0.05</td>
<td>0.781</td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td>77.77%</td>
<td>75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Low adherence</strong></td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td>22.2%</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>36</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Percent</strong></td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In Telmisartan +Cilnidipine group 77.7% patients were showed medium adherence and 22.2% showed low adherence. In Telmisartan +amlodipine 75% showed medium adherence and 25% showed low adherence. The p-value is 0.781. So this difference is not significant at p <0.05.

**DISCUSSION**

The present study was conducted to determine which calcium channel blocker (amlodipine/Cilnidipine) is more effective with angiotensin receptor blocker (Telmisartan) in having positive impact on renal and lipid parameters. In Telmisartan Cilnidipine group, 18(50%) patients were diabetic and 18(50%) were non diabetic. In Telmisartan amlodipine group, 20 (55%) were diabetic and 16(44.4%) were non diabetic.

- On consultation, mean total cholesterol in Telmisartan+Cilnidipine was 176mg/dl, after 3 months it remained same. In Telmisartan +amlodipine group mean total cholesterol was 161 mg/dl and after 3 months it also remained same(p=1,not significant, p<0.10)
- On consultation mean of triglyceride in Telmisartan +Cilnidipine group was 156 mg/dl, which was significantly reduced to 106mg/dl. In Telmisartan +amlodipine group mean of 158 mg/dl on consultation was reduced to 147 mg/dl. On comparison, Telmisartan+Cilnidipine group significantly (p=0.06, p<0.10) reduced triglycerides than Telmisartan+Amlodipine group after followup period. Cilnidipine have a greater lipid lowering effect than the amlodipine.
- On consultation, mean of HDL in Telmisartan +Cilnidipine group was 45.69 mg/dl and after 3 months it was 45.7mg/dl. In Telmisartan+amlodipine group mean of HDL was 49.44 mg/dl and after 3 months it was 49.33mg/dl (p=0.99, not significant, p<0.10).
- On consultation, mean LDL in Telmisartan +Cilnidipine group was 93.3 mg/dl, and after 3 months it’s level was 93.2mg/dl. In Telmisartan +amlodipine group mean of LDL was 94.9 mg/dl and after 3 months it level was 95 mg/dl (p=1, not significant, p<0.10).
- On consultation, mean of Creatinine in Telmisartan +Cilnidipine group was 1.758mg/dl and after 3 months it was reduced to 1.144 mg/dl. In Telmisartan+amlodipine group mean of Creatinine was 1.008mg/dl and it was reduced to 1.02 mg/dl. Both the combination reduced serum creatinine level. But on comparison, reduction in Serum Creatinine between Telmisartan+Cilnidipine group and Telmisartan +Amlodipine group, was not significant (p=0.8108, not significant, p<0.10).
On consultation, mean of eGFR in Telmisartan +Cilnidipine group was 38.08 ml/min/1.73 m² and it was significantly increased to 62.39 ml/min/1.73m². On consultation, in telmisartan +amlodipine group mean of eGFR was 80.33 ml/min/m² and it was increased to 83.7 ml/min/m.². Egfr was significantly (p=0.07885, p<0.10) increased by Telmisartan+Cilnidipine group than Telmisartan+amlodipine group after 3 months. Cilnidipine have more renoprotective effect than amlodipine.

On consultation mean of potassium in Telmisartan +Cilnidipine group was 4.14mEq/L and it was increased to 4.34 mEq/L. On consultation mean of potassium in Telmisartan +amlodipine group was 4.05 mEq/L and it was increased to 4.26 mEq/L (p=0.997, not significant at p<0.10).

Medication adherence was measured by using Morisky medication adherence scale -8. Out of 36 patients in Telmisartan +Cilnidipine group, 28 (77.77%) patients showed medium adherence and 8 (22.2%) patients showed low adherence. Out of 36 patients in Telmisartan +amlodipine group 27 (75%) patients showed medium adherence and 9 (25%) patients showed low adherence.

CONCLUSION
Hypertension is defined as a condition in which blood pressure is elevated. It is the main risk factor for cardiovascular disease. Angiotensin receptor blocker and calcium channel blocker combination are one of the therapies used in hypertension. This combination have greater effectiveness than monotherapy. The effect of this combination on renal function, lipid profile and potassium level were studied in this study. This study shows that Telmisartan +Cilnidipine combination significantly reduces triglyceride level than Telmisartan +Amlodipine group. In case of renal function, Telmisartan + Cilnidipine significantly increases eGFR than Telmisartan+ Amlodipine group and in the case of serum creatinine, Telmisartan + Cilnidipine reduces creatinine level more than Telmisartan +Amlodipine but on comparison the difference is not significant. In both combinations, potassium level were increased but on comparison the difference in increase is not significant.

Based on this study, Telmisartan +Cilnidipine combination is more effective than Telmisartan +Amlodipine combination in terms of renal function and lipid profile.
ACKNOWLEDGEMENTS

Authors are thankful to their guide Mrs. Jeenu Joseph, assistant professor, department of pharmacognosy, pushpagiri college of pharmacy, thiruvalla for her suggestions and indispensable mentorship. They express heartfelt thanks to their esteemed co-guide Dr. sajan ahamad, assistant professor, department of cardiology, pushpagiri college of pharmacy, thiruvalla and they consider it as a great honour to have had the opportunity to work under such an eminent physician.

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