A Pharmacoeconomic Analysis of Metoprolol and Nebivolol - A randomized trial Type of Manuscript: original research article

Dr. Rajkumar Arya¹, Dr Anita Arya², Dr Dharmesh Chandra Sharma², Dr. Arun Kumar Shrivastava³, Dr. Manoj Indurkar⁴ and Dr. Dinesh Kumar Jain⁵

1. Department of Pharmacology, G.R. Medical College, Gwalior India
2. Department of Pathology, G.R. Medical College, Gwalior India
3. Department of Pharmacology, Gandhi. Medical College, Bhopal India
4. Department of Medicine, S.S. Medical College, Rewa India
5. Department of Pharmacology, Bundelkhand Medical College, Sagar India

* Corresponding author: Dr. Anita Arya

Received 11 November 2019; Accepted 27 November 2019

Abstract:
Background: Cost of any drugs can not only judge by simple their price but at the same time efficacy, safety and quality of drug itself determined the actual cost of a drug.
Aims and Objectives: Aim of the present study is to compare the cost-effectiveness and safety of Nebivolol and Metoprolol in order to reduce blood pressure.
Materials and Methods: The present study includes a total of 90 randomly selected patients with the age ranges from 25 to >65 years (mean= ±12). The drug Metoprolol and Nebivolol is given to the 56 and 34 randomly selected patients respectively to observe the effect and tolerability of drug in respect to their costs. Cost effectiveness was calculated and compared by 1mm fall of Hg by both drugs. Safety and effectiveness was observed clinically.
Results: In this present study we found that the Nebivolol is more cost effective, tolerable and safe, as compare to Metoprolol in reducing 1mmHg blood pressure.
Conclusions: In the present study we concluded that Nebivolol is Pharmacoeconomically better drug than Metoprolol. This may affect the patients economically in long term use.
Keywords: Hypertension, Pharmacoeconomic, Efficacy, Cost-effectiveness

I. INTRODUCTION:
Hypertension (HTN) or High Blood Pressure (HBP) is a never ending chronic medical condition where blood pressure in the arteries is persistently elevated [1]. Persistently elevated blood pressure is the major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral vascular disease, vision loss, chronic kidney disease and dementia. [2, 3, 4, 5]. High blood pressure is classified as primary (essential) hypertension and secondary hypertension [6]. In about 90-95% cases of blood pressure, essential hypertension is a major risk factor for coronary artery disease (CAD), cardiac failure and renal insufficiency due to nonspecific lifestyle and genetic factor [6,7,8], while secondary hypertension contributes only 5-10% cases due to identifiable underlying diseases [6]. Beta Adrenoreceptor blocker is the only drug which can be safely used in the treatment of cardiac as well as non-cardiac diseases. As per the Registrar General of India and Million Death Study investigators (2001-2003), cardiovascular disease (CVD) was the largest cause of deaths in males (20.3%) as well as females (16.9%) and led to about 2 million deaths annually [9]. In India, 23.10% men and 22.60% women over the age of 25 years suffer from hypertension [9]. Treating systolic blood pressure (SBP) and diastolic blood pressure (DBP) to targets that are <140/90 mmHg is associated with a decrease in CVD complications [10]. Blood pressure (BP) reductions of 10 mmHg systolic or 5 mmHg diastolic are associated with a 33-48% reduction in stroke and a 17-27% reduction in coronary heart disease (CHD) events [11]. The comorbidities, high prevalence rates, and the chronic nature of hypertension generate substantial economic burden for both the patient and the healthcare system [12]. Previous research has shown that systematic control of blood pressure can result in considerable cost savings [13,14].

Metoprolol is the cardio-selective Beta-1-adrenoreceptor blocker traditionally used to treat hypertensive patients particularly in developing countries such as India. A new highly selective Beta-1-blocker, Nebivolol, has the standard beta-blocking effects, but also produces blood vessel relaxation (vasodilatation), probably through increased secretion of the vasodilator nitric oxide resulting in coronary and peripheral vascular
vasodilatation, thereby, a reduction in peripheral resistance and counteraction of endothelial dysfunction and additionally, an increase in stroke volume, associated with a reduction in vascular resistance, resulting in a maintained cardiac output despite reduced heart rate\cite{15,16,17,18,19}. Studies indicate that Nebivolol, unlike most beta-blockers, does not cause constriction of peripheral blood vessels, and is associated with improved heart function\cite{2}. Studies suggest that it is also less likely to cause fatigue\cite{3}.

Therefore, the present study was conducted with the purpose of comparing the cost-effectiveness of standard doses of Nebivolol and Metoprolol in terms of reduction in 1mm of Hg of blood pressure per day with the secondary objective of comparing the overall efficacy and safety of the two drugs in order to determine the better drug in totality.

II. MATERIALS AND METHODS:

The present prospective observational study was conducted in department of pharmacology, S.S.Medical College and associated S.G.M.Hospital, Rewa from a period of June 2004 to October 2006. A total of 90 hypertensive patients were randomly selected for the study those fulfilling the inclusion/ exclusion criteria. Mean age of the patients were 45±12 SD (with the ranges 25 to >65 yrs.). Written informed consent was taken from all the patients, those were included in the study.

The inclusion criteria

(1). Old or new consented hypertensive patients were selected for the study.
(2). Patients, those were being treated by antihypertensive drugs (cardio selective beta blockers),

The exclusion criteria

Patients who have history of rheumatic heart disease, stroke, recent myocardial infarction (<6month duration), allergic reaction to the antihypertensive drugs, systolic hypertension >200 mm of Hg were excluded from the study.

All the selected patients were grouped in Group I & II and treated with cardio-selective beta blocker; Metoprolol and Nebivolol respectively. The Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) was recorded by standard mercury sphygmomanometer monthly up to the period of 6 months. During each visit to the outpatient department, patients were asked for adverse reaction or any change in their routine life activity related to drugs as well as cost of the drugs weather it gives additional economic burden to the patient.

All data were collected, tabulated, summarized and compared statistically by frequency distribution and percentage proportion. Chi square test were applied to know the significant ($p$ value) ratio of difference statistically by using software EpiCalc 2000.

III. RESULTS:

A total of 90 patients were selected for the study. First Group drug (Metoprolol) was used in 56 patients and second group Drug (Nebivolol) was used in 34 patients and their male: female distribution is summarized in table no 1 and figure no1 which is statistically significant.

<table>
<thead>
<tr>
<th>Table No. 1: Gender Distribution among drug groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>I (Metoprolol)</td>
</tr>
<tr>
<td>II (Nebivolol)</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>
A Pharmacoeconomic Analysis of Metoprolol and Nebivolol - A randomized trial Type of...

The average age of the patients in the study was 45 years, ranges from 25 to >65 years, statistically significant ($p<.05$) shown in the Table No. 2 and figure No. 2.

Table No. 2: Age groups in the study

<table>
<thead>
<tr>
<th>Age-Group → Group</th>
<th>Total</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>56</td>
<td>9</td>
<td>19</td>
<td>13</td>
<td>11</td>
<td>4</td>
<td>0.029081</td>
</tr>
<tr>
<td>Group II</td>
<td>34</td>
<td>2</td>
<td>11</td>
<td>12</td>
<td>3</td>
<td>6</td>
<td>0.016086</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>11</td>
<td>30</td>
<td>25</td>
<td>14</td>
<td>10</td>
<td>0.001298</td>
</tr>
</tbody>
</table>

In group I (n=56, 37.83 %) patients and in Group II (n=34,22.97 %) patients receiving Metoprolol 50 mg /day and Nebivolol 5 mg/day to control blood pressure respectively.

In our study we found that Nebivolol significantly reduces SBP (from 166.12±15.9 to 137.29±10.20), DBP (from 97.24±9.93 to 83.06±4.33) and MAP (from 119.60±8.08 to 101.14±6.01) at a dose given to the selected patients in comparison with the drugs Metoprolol which reduces the SBP (from 155.79±16.9 to
137.89±9.97) DBP (from 99.36±8.17 to 83.96±4.55) and MAP (from 118.16±9.73 to 102.06±5.93) to their respective group. Findings are summarized in table No. 3 and Figure No. 3.

![Gradual Reduction in Blood Pressure Between Groups](image)

**Figure No.3:** Fall in different Blood pressures among drug groups.

A total of 5 patients were showed adverse drug reactions in both groups together. In group I, three patients (Symptoms; nightmare and constipation) and group II, 2 patients (Symptoms: fatigue) had complaint of drug reaction. Findings are summarized in table No 3.

<table>
<thead>
<tr>
<th>ADR</th>
<th>Group I (n=56)</th>
<th>Group II (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nightmare</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E. dysfunction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

In our study we found that Nebivolol reduces SBP 28.83 mmHg and the Metoprolol reduces SBP 17.9 mmHg after 6 months of treatment. The cost of treatment with both the drugs in 6 months during the study period is equal but total cost of reducing 1 mm Hg blood pressure for Nebivolol and Metoprolol was 30 and 50 Rs (INR) respectively.

---

35
A Pharmacoeconomic Analysis of Metoprolol and Nebivolol - A randomized trial Type of.. 

Table no 4. Total Cost of Drugs after 6 months of treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>Drugs</th>
<th>Average cost/Tablet (Approx)</th>
<th>Total Cost of 6 month duration</th>
<th>A.D. R</th>
<th>B.P</th>
<th>At Beginning mmHg</th>
<th>After 6 Month mmHg</th>
<th>Total fall of BP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Metoprolol</td>
<td>5 Rs/-</td>
<td>900 Rs/-</td>
<td>5.36%</td>
<td>MSBP</td>
<td>155.79</td>
<td>137.89</td>
<td>17.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MDBP</td>
<td>99.36</td>
<td>83.96</td>
<td>15.4</td>
</tr>
<tr>
<td>Group II</td>
<td>Nebivolol</td>
<td>5 Rs/-</td>
<td>900 Rs/-</td>
<td>5.88%</td>
<td>MSBP</td>
<td>166.12</td>
<td>137.29</td>
<td>28.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MDBP</td>
<td>97.24</td>
<td>83.06</td>
<td>14.18</td>
</tr>
</tbody>
</table>

From the questionnaires filled during follow up visit of patients at 1, 3 and 6 months and its findings, it was found in our study that Nebivolol has better efficacy, tolerability than Metoprolol. Nebivolol due to better tolerability and less side effects has not hampered the routine activity of patients than Metoprolol. Findings are summarized in Table No. 4.

IV. DISCUSSION:

Cost of any drugs can not only judge by simple their price but at the same time efficacy, safety and quality of drugs itself determined the actual cost of a drugs. It is estimated that in patients with stage 1 hypertension (SBP 140-159 mmHg and/or DBP 90-99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years of therapy will prevent 1 death for every 11 patients treated. In the added presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death [20]. Numerous classes of antihypertensive agents are available, and B-blockers were among those previously recommended as a first-line treatment option in patients with uncomplicated, mild to moderate essential hypertension [21, 22, 23, and 24].

A study carried out by Christine Espinola-Klein et al [25] to evaluate the effects and tolerability of Nebivolol in comparison with Metoprolol in these patients. In conclusion, β-blocker therapy was well-tolerated in patients with peripheral vascular disease and arterial hypertension during a treatment period of 1 year. In the direct comparison, there was no significant difference between Nebivolol and Metoprolol [25]. A meta-analysis carried out by Van Bortel LM et al. to evaluate the efficacy and tolerability of Nebivolol compared with other anti-hypertensive drugs. Twelve randomized controlled studies were included in the study where the dose of Nebivolol 5 mg once daily was compared with the recommended clinical doses of other antihypertensive drugs (n = 9), placebo (n = 2), and both (n = 1). Although not definitive, this meta-analysis suggests that Nebivolol 5 mg is likely to have advantages over existing antihypertensive and may have a role in the treatment of hypertension [26] which further favors our study. A similar study done by Patel R.S. 2014 also revealed that the Nebivolol is more efficacious and cost effective than Metoprolol which further strengthen our study [27].

A study carried by Sonkar S.2015 found that the reduction in SBP and DBP was significant (<0.05) within the group whereas on comparison between the both groups, the difference was insignificant (>0.05) [28].

In another similar study by Uhlíř MF et al., 16 out of 82 (20%) and 25 out of 73 (34%) patients reported adverse events while receiving Nebivolol 5 mg once daily or Metoprolol 100 mg twice daily, respectively [29], while in our study 2 out of 34 (5.88%) and 3 out of 56 patients (5.36%) were reported adverse drug reaction. Similar found in our study, however, the cost of Nebivolol per tablet is higher than that of Metoprolol per tablet which discourages the preference of the former over the latter.

So it is important to administer drugs that are cost-effective and have minimal adverse effects. This is particularly important in a developing country like India, where, the increasing cost of long-term therapy is often a significantly limit the patient compliance.

V. CONCLUSIONS:

This pharmacoeconomic study was carried out for a comparative evaluation of the cost effectiveness of Nebivolol and sustained released Metoprolol succinate in uncomplicated hypertensive patients. There was a statistical as well as clinically significant difference in the efficacy of both the drugs. In this comparative study we found that Nebivolol has better efficacy than Metoprolol in terms of reducing both systolic as well as diastolic blood pressure. In this study, it was evident that Nebivolol had less adverse effects and ensures a better quality of life than Metoprolol.
REFERENCES


