Original Article

Comparison of Effect of Enalapril and Losartan Monotherapy on Quality of Life and Safety of Stage 1 Hypertensive Patients

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Abstract

An open label randomized controlled study was conducted to compare the quality of life (QoL) and safety of newly diagnosed stage 1 hypertensive patients randomized into two groups of 30 receiving either enalapril 5 mg or losartan 50 mg per-oral once daily for three months. QoL was assessed at the baseline and at the end of study using SF-36v2 health care questionnaire. Adverse drug reactions (ADRs) were monitored. Investigations at baseline were compared with those after intervention.

Pre & post-intervention QoL transformed scores within each group and change in the same between two groups were analyzed using paired and unpaired t-test respectively.

Transformed scores of role limitation due to energy/fatigue, emotional well being and general health domains improved significantly in both treatment groups. Scores of bodily pain improved significantly (p=0.0008) in losartan group only.

Results were not significantly different between two groups (except for bodily pain). No serious ADR was reported.

Introduction

Hypertension is the most common cardiovascular disease associated with risk of strokes, cardiac failure and renal insufficiency (1). Role of renin angiotensin aldosterone system (RAAS) in pathogenesis of hypertension is well established (2). Angiotensin II, through its action on AT1 receptors in the blood vessels causes potent vasoconstriction and the secretion of aldosterone from adrenal glands resulting in increase in blood pressure and remodeling of heart and blood vessels (2). Reduced levels of angiotensin II through inhibition of Angiotensin Converting Enzyme (ACE) caused by enalapril whereas prevention of action of angiotensin II on AT1 receptor by losartan, ultimately results in the reduction in the blood pressure (2).

In clinical studies, enalapril & losartan have been found to have similar efficacy in lowering the blood pressure in stage 1 hypertension (3-7).
Safety studies encompassing these medicines reported marginal favorable safety profile of losartan as compare to enalapril (2). In such situation, decision to choose either enalapril or losartan may also depend on effect of drugs on patient’s quality of life (QoL). Studies comparing the QoL of patients receiving two antihypertensive treatments are lacking in India. Hence, this study was planned to generate data on the quality of life and safety of the patients taking either enalapril or losartan for stage 1 hypertension.

Methods

Study population

Open label, randomized, prospective clinical study was conducted on 60 subjects attending outpatient department of Internal Medicine between November 2011 and March 2013, fulfilling the inclusion criteria of stage 1, uncomplicated, essential hypertension having mean sitting diastolic blood pressure (MSDBP) between 90 mmHg and 99 mmHg and age >18 years. Exclusion criteria for the patients were history of hypertensive encephalopathy, cerebrovascular accident, myocardial infarction in the previous three months, heart failure in the previous six months, patients with symptomatic heart failure, severe angina pectoris, 2nd or 3rd degree heart block, known case of significant hepatic, renal or gastrointestinal disease, patients who had taken a medication that could affect blood pressure within 14 days of randomization, known history of allergy to enalapril and/or losartan or their any component, pregnant women and patients whose chest X-Ray and electrocardiogram was suggestive of cardiomegaly and coronary artery disease. Patients who agreed to participate in the study by giving written informed consent were randomized by block randomization into two groups to receive either enalapril 5 mg (Canapril-5) or losartan 50 mg (Angizaar-50) PO (peroral) once daily. The patient compliance was ensured by pill count method at each follow up visit. Study was approved by Institutional Ethics Committee for human research. Confidentiality of patients was maintained adequately.

Assessment of quality of life and safety

The QoL of the patients receiving either enalapril or losartan treatments was assessed using “Quality of life health care questionnaire” (SF-36v2 form) at baseline and at the end of three months treatment. SF-36v2 form contained 36 questions grouped into eight health domains (physical functioning, role limitation due to physical health, role limitation due to emotional problem, energy/fatigue, emotional well being, social functioning, bodily pain and general health). Scores of each item and health domain were recorded and converted into transformed scores for analysis. Clinical examination of the patients including vitals and ADRs (adverse drug reactions) were recorded at every follow-up visit (at the end of 1st, 2nd and 3rd month). The causality assessment of the ADRs was done using WHO probability scale (8).

Hematological and biochemical investigations

All the patients were investigated for hemogram, liver function test (LFT), kidney function test (KFT), urine routine & microscopy, chest X-Ray PA view and ECG at the baseline and at the end of 3 months treatment.

Statistical consideration

Sample size was calculated using software PS version 3.1.2 considering normal distribution of the response from previous data, standard deviation of 27 for change in QoL transformed scores, true difference in mean score change of two groups to be 20, type 1 error or alpha value of 0.05 and power of the study 80%. Transformed scores of QoL for various health domains, values of biochemical and hematological parameters at the baseline and at the end of enalapril/losartan treatment within both the groups were compared using paired Student’s t-test. The differences of pre and post intervention QoL transformed scores (i.e. change in QoL) of respective health domains in enalapril and losartan treatment groups were compared using unpaired Student’s t-test. ‘Graphpad®’ software was used for analysis of the data.
Results

A total of 30, stage 1 hypertensive patients enrolled in each group (enalapril and losartan) completed the study. Baseline demographic parameters, body mass index and mean BP of recruited patients were as per Table I. MSDBP was well maintained below 90 mm Hg in all patients with both treatments.

QoL of patients within enalapril treatment group

Enalapril treatment significantly ($p=0.01$) improved the score of 2nd health domain (i.e. role limitation due to physical health). Increase in scores of role limitation due to emotional problems and physical health domain were not statistically significant ($p=0.06$ and 0.054 respectively) (Table II).

Similarly, energy/fatigue health domain of QoL improved significantly ($p=0.0007$) after 3 months of enalapril treatment. Enalapril also improved the emotional well being of the patients and this rise in QoL was statistically significant ($p=0.0009$). Enalapril did not influence the social functioning and pain domain significantly ($p=0.09$ and 0.64 respectively). General health transformed scores raised significantly ($p=0.001$) (Table II).

QoL of patients within losartan treatment group

Baseline scores of physical functioning and role limitation due to physical health domain in losartan group improved significantly ($p=0.01$ and 0.008 respectively). Scores of role limitation due to emotional problems was raised but it was statistically insignificant ($p=0.07$).

Energy/fatigue health domain ($p=0.02$) and emotional well being of the patients ($p=0.005$) also significantly improved after 3 months of losartan treatment. Losartan did not influence the social functioning domain significantly ($p=0.09$). Improvement in pain domain ($p=0.0008$) and general health ($p=0.005$) transformed score were significantly better after 3 months of treatment (Table III).

Comparison of change in QoL of patients between two treatment groups

The mean changes in transformed scores for all health domains except bodily pain between two treatment groups were statistically comparable. The differences in pre and post-treatment scores of bodily pain domain among two groups was significantly ($p=0.001$)
better in losartan treatment group than that in enalapril treatment group (Table IV).

**Comparison of investigations within the enalapril treatment group**

Enalapril did not show significant change in any of the blood investigation (Table V).

In enalapril treated group, one patient showed reduction in proteinuria from baseline grade +3 to +1 with decrease in glycosuria from +1 to undetected level after 3 months of treatment. Another patient in this group showed reduction in proteinuria from baseline value +1 to undetected level. Post enalapril treatment ECG and X-ray chest findings remained unchanged.

**TABLE IV**: Inter-group comparison of change in QoL transformed scores of various health domains.

<table>
<thead>
<tr>
<th>Domains</th>
<th>Differences of pre and post treatment scores in two treatment groups (Mean±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enalapril (n=30)</td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>31.67±86.59</td>
<td>0.53</td>
</tr>
<tr>
<td>Role limitation due to physical health</td>
<td>23.33±46.39</td>
<td>0.41</td>
</tr>
<tr>
<td>Role limitation due to emotional problems</td>
<td>12.50±34.59</td>
<td>0.59</td>
</tr>
<tr>
<td>Energy/fatigue</td>
<td>25.83±37.42</td>
<td>0.94</td>
</tr>
<tr>
<td>Emotional well being</td>
<td>35.83±52.80</td>
<td>0.25</td>
</tr>
<tr>
<td>Social functioning</td>
<td>6.67±20.69</td>
<td>0.87</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>-2.17±25.08</td>
<td>0.001</td>
</tr>
<tr>
<td>General health</td>
<td>33.33±50.57</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Losartan (n=30)</td>
<td></td>
</tr>
</tbody>
</table>

**Comparison of investigations within the losartan treatment group**

In losartan group, deterioration in liver function including serum albumin, globulin, AST and ALT levels was recorded. Mean serum albumin and total bilirubin levels were significantly reduced in comparison to baseline values (p=0.05 and 0.01 respectively) (Table VI).

Losartan did not show any effect on urine routine and microscopic examination. Post-treatment ECG and chest X-ray also remained unchanged.

**Safety**

Both the treatments were well tolerated. None of the patients reported any serious adverse event in both the groups. In enalapril group, one patient reported lightheadedness, which resolved itself within few days without requiring any modification of the dose or treatment had ‘possible’ causality assessment between the event and enalapril treatment.

**Discussion**

WHO defines quality of life as individuals’ perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns (9). Researchers at the University of Toronto’s Quality of Life Research Unit defined quality of life as “The
degree to which a person enjoys the important possibilities of his or her life” (10).

QoL is a humanistic outcome, and consequences of the disease and/or its treatment perceived and experienced by the patient (11, 12). These patient-reported outcomes included self-assessment of health status, symptom experienced, treatment satisfaction/dissatisfaction and well being (11).

In our study, patients in enalapril treatment group showed significant improvement in role limitation due to physical health, energy/fatigue, emotional well being and general health. Whereas in losartan treatment group, patients’ transformed scores in physical functioning, role limitation due to physical health, energy/fatigue, emotional well being, bodily pain and general health domain were increased significantly. Comparison of QoL outcomes between the two groups in the present study showed no significant difference in improvement in transformed scores for any of the health domain except bodily pain, for which improvement was significantly ($p<0.001$) better in losartan treatment group. De Rosa et al. in a double blind placebo run-in study on stage 1 hypertension patients studied the effects of chronic ACE inhibition by enalapril and AT1 receptor blockade by losartan on QoL using self administered questionnaire and reported no difference between two treatments in terms of patient satisfaction on quality of life (5), though there was improvement in QoL within each group. Preclinical studies have suggested analgesic activity of angiotensin II, when administered intracerebroventricularly (13, 14, 15).

In the present study bodily pain was the only health domain which deteriorated with enalapril treatment although not significantly. It could mean enalapril caused more pain perception. It is also hypothesized that algesic effect of enalapril could be due to its antihypertensive action as hypertension causes hyperalgesia, and/or some other pharmacodynamic action (13). Moreover, enalapril acts as kininase II inhibitor and reduces degradation of bradykinin which may also contribute to induce pain (13). Since ACE-inhibitors inhibit the conversion of angiotensin I to angiotensin II, hence may increase the pain perception because angiotensin II may exert analgesic action probably through nucleus tractus solitarii and area postrema, which are the anatomic regions to control BP and pain perception (13, 16, 17). On the contrary, a preclinical study reported that angiotensin II antagonized the analgesic effect of morphine and electropuncture induced analgesia, suggesting algesic action of angiotensin II (13, 16, 18).

In this study, enalapril was found to be better than losartan with regard to QoL related to role limitation due to physical health, role limitation due to emotional problems, energy/fatigue, social well being and general health (improvement was more in enalapril group although difference in improvement between two groups was not statistically significant). Another study conducted to compare the quality of life and dry persistent cough among the mild to moderate hypertensive patients treated with either eprosartan

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**TABLE VI**: Comparison of baseline biochemical parameters of patients receiving losartan with their post-treatment values (i.e. after 3 months treatment).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Losartan group</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre treatment</td>
<td>Post treatment</td>
</tr>
<tr>
<td></td>
<td>Hb (mmol/L)</td>
<td>07.86±0.78</td>
</tr>
<tr>
<td></td>
<td>TLC (10$^9$/L)</td>
<td>05.83±1.97</td>
</tr>
<tr>
<td></td>
<td>Platelets (10$^9$/L)</td>
<td>192.19±78.22</td>
</tr>
<tr>
<td>Liver function test (Mean±SD)</td>
<td>Albumin (g/L)</td>
<td>34.2±3.8</td>
</tr>
<tr>
<td></td>
<td>Globulin (g/L)</td>
<td>23.1±4.2</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin (µmol/L)</td>
<td>14.36±7.18</td>
</tr>
<tr>
<td></td>
<td>AST (U/L)</td>
<td>33.39±7.97</td>
</tr>
<tr>
<td></td>
<td>ALT (U/L)</td>
<td>38.47±13.10</td>
</tr>
<tr>
<td>Kidney function test (Mean±SD)</td>
<td>Urea (mmol/L)</td>
<td>09.25±2.27</td>
</tr>
<tr>
<td></td>
<td>Creatinine (µmol/L)</td>
<td>67.18±18.56</td>
</tr>
<tr>
<td></td>
<td>Na$^+$ (mmol/L)</td>
<td>137.07±3.32</td>
</tr>
<tr>
<td></td>
<td>K$^+$ (mmol/L)</td>
<td>04.23±0.44</td>
</tr>
</tbody>
</table>
or enalapril and reported small but significant improvement in the measures of self-control and total Psychological General Well being Index in patients taking enalapril (19). In their three months study Malmqvist, Karin et al. compared the efficacy, effect on subjective symptoms and QoL of AT1 antagonist candesartan, ACE inhibitor enalapril and diuretic hydrochlorothiazide and found no differences in QoL among three treatment groups (20). In present study, both the treatment groups showed significant improvement in QoL but difference in improvement in most of the health domains between two treatments was statistically insignificant as stated above.

In our study, decreased pain health domain scores were not seen in patients of losartan group, this may be due to probable action of angiotensin II on receptors other than AT1 at central level. This suggested that in a condition where hypertension is associated with pain, losartan may be the preferred option over enalapril, but further studies are advocated to establish this further.

Emotional well being health domain of SF-36v2 questionnaire includes feeling full of life, depression, happiness etc., and was improved in both the treatment groups in current study. In pre-clinical studies ACE inhibitors and AT1 antagonists have exhibited antidepressant activity (21). In humans also there are evidences which suggested that abnormality of RAAS (renin angiotensin aldosterone system) may be weakly associated with depression (22). This suggested that antihypertensive drugs modulating RAAS may alleviate depression also in these patients (22).

Both enalapril and losartan were well tolerated by the patients. Incidence of dry cough and angioedema is said to be 5-20% and 0.1-0.5% respectively (2), but in our study no patient reported these typical adverse effects of ACE inhibitors. The reason might be study population variability, small sample size or short study period. In our study enalapril showed slight deterioration in LFT (serum albumin) but within prescribed guidelines, hence treatment was continued without any modification of the dose.

In our study even losartan treated patients showed post treatment significant reduction in mean serum albumin, which could be due to hepato-toxic property of ARBs (23, 24).

On the other hand pre-clinical studies have reported hepatoprotective effects of enalapril against acetaminophen induced hepato-toxicity in mice (25) and of ARBs in hepatitis C induced liver cirrhosis (26, 27).

In our study, in enalapril group, two patients had baseline proteinuria which was reduced significantly in three months. This beneficial renoprotective effect of ACE-inhibitors may be due to reduction in glomerular capillary pressure both by decreasing arterial BP and by dilating efferent arterioles, preventing proteinuria and glomerular injury by increasing permeability selectivity of filtering membrane (2).

**Study limitations and strength**

Our study is limited by (1) lack of blinding in the study design, (2) short study period (three months) which might not be adequate to detect the long term effect of a treatment on quality of life and safety, (3) recruitment of patients was from single institution so this study didn’t include patients from wider range of population, (4) Moreover the possibility of confounding of results by concomitant medications (pain killers, multivitamins etc.), which may affect one or more QoL health domains, couldn’t be ruled out.

Strength of our study is that it has focused on QoL (and not just safety and efficacy) which encompass a number of factors including these two, for selection of an antihypertensive and it can act as a promoter to conduct such further large double blinded randomized controlled studies.

Controversies raised by this study are whether (1)
enalapril deteriorates the QoL related to pain or it could be beneficial to diabetic patients with autonomic neuropathy (who already suffer from decreased pain sensitivity) (2), Angiotensin II creates a state of hypoalgesia or it antagonizes it (3), AT1 antagonists are hepatotoxic or hepatoprotective.

So this study gives a new direction to conduct research to elucidate the role of enalapril in diabetic patients with regard to pain perception, to confirm and identify the mechanism of effects of losartan on pain related QoL and also to disclose the suspected potential of AT1 antagonists to cause hepatotoxicity.

Conclusion and recommendations

This study shows that both enalapril and losartan treatments improved the QoL regarding most of the health domains individually but the improvement between two groups is not statistically different in most health domains except bodily pain which is better in losartan group. So we can’t conclude superiority of one treatment over other except for pain domain for which losartan appears better. Moreover, the role of enalapril in diabetic patients with regard to pain perception should also be elucidated. To further confirm these outcomes large double blind randomized controlled trials are recommended.

References


