Effect of Losartan and Amlodipine on Heart Rate Variability In Essential Hypertensive Patients

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Abstract

Background: Essential hypertension is characterized by sympathovagal imbalance that is responsible for arrhythmias and sudden cardiac death. Antihypertensive drugs restores sympathovagal balance. Losartan and amlodipine are common antihypertensive drugs. Objective: To compare the effect of losartan and amlodipine on heart rate variability (HRV) in hypertensive patients. Methods: This prospective analytical study was carried out in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from July 2012 to June 2013. For this study, 120 newly diagnosed hypertensive patients without any treatment (group B, age 30-55 years) were selected from the Out Patients Department of cardiology, BSMMU, Dhaka on their first day of visit. 60 apparently healthy normotensive subjects were also studied as control (group A). HRV of the patients were measured both before and after they were treated with two different antihypertensive drugs (losartan and amlodipine) separately. According to the selection of drug these patients were divided into two groups. Group B1 included 60 patients received losartan 50 mg daily and group B2 included 60 patients treated by amlodipine 5 mg daily. They were observed once before the treatment (B1a&B2a) and after 3 months medication (B1b & B2b) and also after 6 months medication (B1c & B2c). For assessing HRV, Mean heart rate (HR), Mean R-R interval, Max/Min R-R interval, SDNN, RMSSD were recorded by a polyrite. Data were compared among before treatment, after 3 months treatment and after 6 months treatment. For statistical analysis ANOVA, independent sample ‘t’ test and paired sample ‘t’ were performed. Results: Mean resting pulse rate, mean heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) were significantly higher (P<0.001) and mean R-R interval, SDNN, RMSSD were significantly lower (P<0.001) in patients before treatment compared to those of healthy normotensive subjects and to the values after treatment. In both drug groups, SDNN, RMSSD, mean R-R interval were found significantly higher after 6 months of treatment compared to their values after 3 months treatment and also close to the values in normotensive subjects. In losartan group RMSSD were found significantly higher (p<0.01) and mean R-R interval, SDNN were found though higher but not significant than the corresponding values in amlodipine treated patients after 6 months treatment. Conclusion: Vagal modulation is decreased in untreated hypertensive patients which is increased by treatment with both losartan and amlodipine but the effect is more pronounced in losartan. The decreased autonomic function was improved better with longer treatment duration.

Key words: Newly diagnosed hypertensive patients, heart rate variability, losartan, amlodipine.

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Introduction
Hypertension is usually defined as persistent blood pressure at 140/90 mm Hg or higher, affects about a quarter of the adult population in many countries. The autonomic nervous system (ANS) plays an important role in the control of arterial blood pressure and heart rate and intimately related to the development of systemic hypertension.

Essential hypertension is associated with altered autonomic nerve function which is characterized by sympathetic overactivity, attenuation of parasympathetic modulation of the heart and overall reduced heart rate variability (HRV). Several studies have identified reduced HRV in essential hypertension. Reduced HRV has been associated with a higher risk for all mortality in survivors of an acute myocardial infarction and sudden cardiac death. The anti-hypertensive drug therapy reportedly can reduce the risk of stroke and coronary heart disease.

Methods
This prospective analytical study was carried out to observe the cardiac autonomic activity by assessing some time domain measures of HRV in 120 adult male hypertensive patients aged 30-55 years in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from July 2012 to June 2013. For comparison 60 apparently healthy normotensive subjects were also studied as control (group A). According to drug and time period of treatment, study subjects were divided into two groups(B1 and B2). GroupB1 included 60 patients received losartan 50 mg daily and B2 included 60 patients received amlodipine 5mg daily. They were observed once before the treatment (B1a & B2a) after 3 months medication (B1b & B2b) and after 6 months medication (B1c & B2c). These patients were selected from the Out Patient Department of Cardiology, BSMMU. Hypertensive patients with history of taking anti-hypertensive drugs, previously diagnosed as hypertension, diabetes mellitus, ischaemic heart diseases, renal disease, psychic disorder and smoking were excluded from the study. After selection, the objectives of the study were explained to all the subjects and their voluntary participation was encouraged. An informed written consent was taken from each subject. The protocol of this study was approved by the Institutional Review Board of BSMMU. Then the subject was prepared for Autonomic Nerve Function Test. Immediately after enrollment, HRV data were recorded before initiating treatment.

In addition to the conflicting result of this two drugs, no study so far compared their effect on HRV. Therefore this study aimed to observe and compare the effect of losartan and amlodipine on HRV in hypertension as well as the time period of the therapy required to achieve their target.
with any antihypertensive drugs. All the autonomic nerve function tests were done in the Autonomic Nerve Function laboratory in the department of Physiology. The subject was kept in supine position in a bed for 15-20 minutes in a controlled laboratory environment. Then all preparations for recording of the Heart rate variability parameters were made by connecting the channels of ECG and a 5 minutes short term recording was taken in resting position. Mean heart rate, Mean R-R interval, Max/Min R-R interval, SDNN, RMSSD were measured by a polygraph.

Then all the patients were requested to attend the Department of Physiology of BSMMU, after 3 months and after 6 months of antihypertensive medication for recording of follow up HRV data. For statistical analysis ANOVA, independent sample ‘t’ test and paired sample ‘t’ were performed.

Results

Anthopometric data of all subjects are given in Table-I.

Mean resting pulse, SBP and DBP were significantly higher in group B1a and B2a compared to those of controls and this values were significantly decreased in group B1b, B1c, B2b and B2c compared to those before treatment. (Table II).

Mean values of mean HR were significantly higher (p<.001) in group B1a and B2a and Mean R-R interval, Max/Min R-R, SDNN, RMSSD were significantly lower(p<0.001) in group B1a and B2a than those of group A. Mean heart rate were significantly decreased (p<0.001) in group B1b, B1c, B2b and group B2c in comparison to their baseline values. In addition this value showed no significant difference when compared between group A and group B1c. Mean heart rate in group B2c was significantly higher (p<0.05) than that of group B1c. Mean values of Mean R-R interval, Max/Min R-R interval, SDNN, RMSSD were significantly increased in group B1b, B1c, B2b, and B2c when compared to those of baseline values. But mean values of SDNN and RMSSD were significantly decreased in group B1c and group B2c compared to those of control group. RMSSD in group B1c was found significantly higher (p<0.003) than that of group 2c (Table III & IV).

Table I : Anthropometric data of all subjects (n=120)

| Group | Age (years) | BMI (kg/m²) |
|-------|-------------|-------------|
| A (n=60) | 42.04±1.134 | 23.24±0.243 |
|        | (30-35)     | (18.59-24.77) |
| B1a (n=60) | 41.64±1.165 | 23.27±0.216 |
|        | (30-35)     | (18.65-24.77) |
| B2a (n=60) | 42.74±1.312 | 23.36±0.198 |
|        | (30-35)     | (18.37-24.74) |

Statistical analysis

A vs B1a vs B2a i 0.296 ns 0.850 ns
A vs B1a o 0.806 ns 0.912 ns
A vs B2a o 0.688 ns 0.688 ns
B1a vs B2a u 0.533 ns 0.748 ns

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. i= independent sample ‘t’ test. o=paired sample ‘t’ test.

SBP = Systolic blood pressure.
DBP =maximum

Group
A = Apparently healthy subject (control)
B = Newly diagnosed hypertensive patients before treatment
B1a = After 3 months treatment with losartan
B2a = After 3 months treatment with amlodipine

*** = p<0.001 ns= non significant (p>0.05)
** = p<0.01 n= number of subjects.
* = p<0.05
### Table II: Baseline measures in different groups (n=120)

| Groups          | Pulse   | Systolic blood pressure | Diastolic blood pressure |
|-----------------|---------|-------------------------|--------------------------|
| A               | 78.15±0.862 | 126.4±0.603               | 73.2±0.515               |
| (93-70)         | (120-135) | (65-80)                 |
| B1a             | 83.55±0.919 | 141.6±0.462               | 91.5±0.295               |
| (95-70)         | (140-155) | (90-98)                 |
| B1b             | 76.37±0.767 | 127.7±0.45               | 77.4±0.510               |
| (90-70)         | (120-135) | (70-85)                 |
| B1c             | 75.33±0.664 | 127.7±0.449               | 76.2±0.476               |
| (87-65)         | (120-135) | (70-85)                 |
| B2a             | 82.33±0.994 | 142.8±0.520               | 91.2±0.265               |
| (95-70)         | (140-155) | (90-95)                 |
| B2b             | 76.95±0.978 | 128.2±0.474               | 77.4±0.545               |
| (90-65)         | (120-135) | (70-85)                 |
| B2c             | 75.10±0.950 | 127.4±0.381               | 76.4±0.429               |
| (85-63)         | (120-130) | (70-80)                 |

**Statistical analysis**

| Comparison | p-value |
|------------|---------|
| A vs B1a   | 0.000*** |
| A vs B1b   | 0.000*** |
| A vs B1c   | 0.000*** |
| B1a vs B1b | 0.000*** |
| B1a vs B1c | 0.000*** |
| B1b vs B1c | 0.252ns  |
| B2a vs B2b | 0.000*** |
| B2a vs B2c | 0.000*** |
| B2b vs B2c | 0.105ns  |

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. ö= independent sample ‘t’ test. Ù=paired sample ‘t’ test.

SBP = Systolic blood pressure.

DBP = Diastolic blood pressure

**Group A** = Apparently healthy subject (control)

**B1a** = Newly diagnosed hypertensive patients before treatment

**B1b** = After 3 months treatment with losartan

**B1c** = After 3 months treatment with losartan

**B2a** = Newly diagnosed hypertensive patients before treatment

**B2b** = After 3 months treatment with amlodipine

**B2c** = After 3 months treatment with amlodipine

* *** = p<0.001

ns = non significant (p>0.05)

** = p<0.01 n= number of subjects.

* = p<0.05
Table III: Simple time domain measures of HRV in different groups (n=120)

| Groups  | Mean heart rate (Beat/min) | Mean R-R interval (sec.) | Max/min R-R interval |
|---------|---------------------------|-------------------------|----------------------|
| A (n=60) | 73.33±0.712               | 0.753±0.12              | 1.75±0.066           |
| B1a     | 84.85±0.895               | 0.693±0.014             | 1.46±0.041           |
|         | (95-70)                   | (1.04-0.571)            | (3.79-1.12)          |
| B1b     | 77.75±0.909               | 0.730±0.10              | 1.71±0.64            |
|         | (90-65)                   | (1.128-0.619)           | (4.99-1.104)         |
| B1c     | 74±0.886                  | 0.748±0.011             | 1.78±0.057           |
|         | (85-63)                   | (1.135-0.551)           | (12.18-7.89)         |
| B2a     | 82.33±0.242               | 0.699±0.010             | 1.58±0.071           |
|         | (99-60)                   | (1.075-0.602)           | (3.39-1.12)          |
| B2b     | 78.92±1.057               | 0.737±0.008             | 1.70±0.051           |
|         | (95-60)                   | (.996-.617)             | (2.80-1.12)          |
| B2c     | 77.13±0.013               | 0.747±0.013             | 1.72±0.052           |
|         | (97-64)                   | (1.128-0.562)           | (3.37-3.7)           |

Statistical analysis

A vs B1a  
A vs B1b  
A vs B1c  
B1a vs B1b  
B1b vs B1c  
B1a vs B1c  
A vs B2a  
A vs B2b  
A vs B2c  
B2a vs B2b  
B2b vs B2c  
B2a vs B2c  

A vs B2a  
A vs B1b  
A vs B1c  

Statistical analysis:

- **p<0.001**
- *p<0.05*
- ns = non significant (p>0.05)
- n = number of subjects.

Data were expressed as mean ± SE, figures in parenthesis indicate ranges.  = independent sample ‘t’ test.
  = paired sample ‘t’ test.
R-R = interval between successive QRS complex (sec)
Max = maximum, Min = minimum

Group A = Apparently healthy subject (control)
B1a = Newly diagnosed hypertensive patients before treatment
B1b = After 3 months treatment with losartan
B1c = After 3 months treatment with losartan
B2a = Newly diagnosed hypertensive patients before treatment
B2b = After 3 months treatment with amlodipine
B2c = After 3 months treatment with amlodipine

Statistical analysis:

- **p<0.001**
- *p<0.05*
- ns = non significant (p>0.05)
- n = number of subjects.
Table IV: Statistical time domain measures of HRV in different groups (n=120)

| Groups | SDNN (ms) | RMSSD (ms) |
|--------|-----------|------------|
| A (n=60) | 78.18±1.95 | 32.69±0.89 |
|         | (99.8-50.09) | (41.89-17.99) |
| B₁a (n=60) | 40.63±2.37 | 24.57±0.521 |
|         | (102.8-15.11) | (32.99-18.76) |
| B₁b | 54.40±2.39 | 26.98±0.392 |
|         | (100.09-26.15) | (34.22) |
| B₁c | 71.42±2.53 | 30.59±0.414 |
|         | (108.1-31.09) | (45.31-23.8) |
| B₂a | 50.97±1.94 | 24.36±0.603 |
|         | (90.8-28.8) | (34.99-15.78) |
| B₂b | 52.4±2.50 | 27.41±0.582 |
|         | (90.15-30.34) | (36.77-20.6) |
| B₂c | 69.48±2.67 | 28.56±0.528 |
|         | (100.9-40.88) | (35.78-22.6) |

Statistical analysis

A vs B₁a **0.000*** 0.000***
A vs B₁b **0.000*** 0.000***
A vs B₁c **0.000*** 0.000***
B₁a vs B₁b **0.000*** 0.001
B₁b vs B₁c **0.000*** 0.008
B₁a vs B₂b *0.010* 0.000***
B₂a vs B₂b 0.524ns 0.004*
B₂a vs B₂c 0.000*** 0.076ns
B₂b vs B₂c 0.000*** 0.000***
B₁a vs B₂c 0.586ns 0.003**

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. δ = independent sample ‘t’ test. Ù = paired sample ‘t’ test.

SDNN = Standard deviation of N-N interval
RMSSD = Square root of mean squared differences between adjacent NN intervals.

Group
A = Apparently healthy subject (control)
B₁a = Newly diagnosed hypertensive patients before treatment
B₁b = After 3 months treatment with losartan
B₁c = After 3 months treatment with losartan
B₂a = Newly diagnosed hypertensive patients before treatment
B₂b = After 3 months treatment with amlodipine
B₂c = After 3 months treatment with amlodipine

Discussion

In this study effects of two antihypertensive drugs losartan and amlodipine on HRV in patients with essential hypertension were studied. HRV was found reduced in hypertensive patients before initiating treatment with losartan and amlodipine compared to normotensive subjects which agrees to other investigators. The effect of losartan and amlodipine on HRV was observed after 3 months of medication and then again after 6 months of medication. It was observed that HRV was significantly increased after 3 months in losartan groups but though increased but not significant in amlodipine treated patients. For losartan, similar observation was made by Carpia et al25 and Chern et al.20 whereas others did not find this effect. For amlodipine, results of this study were almost similar to other investigators but they studied this effect with less duration of treatment.27,31,32 After 6 months of treatment with these two drugs both losartan and amlodipine, HRV were found significantly increased compared to their corresponding values after their 3 months of treatment. Chern et al.20 observed similar effect of losartan after 6 months but they did not find any significant difference compared to 3 months treatment duration. No publications are available to compare this effect for amlodipine after 6 months treatment. The values of HRV after 6 months of treatment in both drugs were found close to the values of controls. Similar investigations found relative improvement of HRV after few weeks of treatment with both the drugs but it was still remained lower than the controls.25-27

In this study, time domain result reflect lower cardiac vagal modulation in untreated patients which was found significantly improved with both drugs after 3 and 6 months treatment. On further analysis the effect of losartan was found more pronounced than amlodipine improving the cardiac vagal activity which is supported by significantly higher value of RMSSD and lower
value of mean HR in losartan treated patients. In addition, 6 months duration of treatment was found more effective than 3 months treatment which is supported by the facts that HRV values were close to controls after 6 months treatment.

Various mechanisms has been proposed for the improvement of HRV in hypertensive patients after treatment with losartan and amlodipine. Hypertension has been found associated with altered cardiac autonomic function evidenced by reduced HRV, sympathetic overactivity and low Baroreflex sensitivity (BRS).27,28,33

Losartan acts as Angiotensin II type-I receptor (AT$_1$) blocker which antagonizes the suppressor effect of elevated Angiotensin II on BRS thereby restore the sympathovagal by increasing BRS. Furthermore, it increases NO production from vascular endothelium and neuron which facilitate the regulation of BRS and HRV in losartan treated hypertensive patients.33,34

Amlodipine is a calcium channel antagonist, which inhibits norepinephrine release from the noradrenergic nerve terminals by blocking its calcium influx thus reducing sympathetic overactivity. This drug also suppresses Aldosterone secretion from adrenal glomerulosa cortex.35

Though both the drugs lower blood pressure by counter acting excess neural activity or BRS and also by suppressing adrenocortical hormone but their exact mechanisms for improvement of HRV after treatment with losartan and amlodipine in hypertensive groups can not be elucidated from this type of study. Moreover, the cause of the difference of their effect on cardiac autonomic function can not be anticipated from this study. However, the mentioned mechanisms for these two antihypertensive drug may have some influence on the improvement of cadiac autonomic activity in these patients after treatment with losatan and amlodipine. The outcome of the study suggests a positive relation and duration of treatment of these two antihypertensive drugs with improvement of HRV.

Conclusion
Impairment of cardiac autonomic nervous activity occurred in untreated hypertensive patients which was improved by both losartan and amlodipine and in particular losartan was found more effective. The improvement of impaired cardiac autonomic function is better with longer duration of treatment.

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