Effect of Losartan and Atenolol on Heart Rate Variability in Newly Diagnosed Essential Hypertensive Patient.

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Abstract:

Background: Essential hypertension is associated with altered autonomic function[1]. Essential hypertension is treated with drugs which modify the sympatho- parasympathetic balance. Losartan (angiotensin II receptor blocker) and atenolol (beta blocker) is commonly used antihypertensive drugs. **Objective:** To evaluate the effect of antihypertensive drugs on heart rate variability (HRV) in patients with essential hypertension. **Methods:** This prospective observational study was carried out in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from July 2012 to June 2013 on 120 newly diagnosed hypertensive patients without any medication (group B, age 30-55 years). They were selected from the Out Patients Department (OPD) of cardiology, BSMMU, Dhaka. Age, sex and BMI matched 60 apparently healthy normotensive subjects were also studied as control (group A). Based on treatment, these study subjects were divided into two groups (B1 and B2). Group$B1_a$ included 60 patients received losartan 50 mg daily and B_{2a} included 60 patients received atenolol 50mg daily .They were observed once before the treatment (B_{1a}&B_{2a}), after 3 months medication ($B1_b$ & $B2_b$) and after 6 months medication ($B1_c$ & $B2_c$). For assessing HRV, Mean heart rate, 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' test were performed. **Results:** Mean resting pulse rate, mean heart rate, systolic blood pressure, diastolic blood pressure were significantly higher and mean R-R interval, Max/Min R-R interval, SDNN, RMSSD were significantly lower in newly diagnosed hypertensive patients in comparison with that of healthy normotensive subjects and after treatment. In both groups SDNN, RMSSD, mean R-R interval were found significantly higher after 6 months of treatment compared to their values after 3 months treatment. Again these values were found close to the values in normotensive subjects. In addition, mean heart rate was found significantly lower in atenolol treated patients than those of controls. Again in atenolol group these values were found significantly higher than the corresponding values in losartan treated patients after 6 months treatment. **Conclusion:** Reduced cardiac vagal tone occurs in newly diagnosed hypertensive patients which is improved by both losartan and atenolol and in particular atenolol was found more effective.

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

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Introduction:

Hypertension has been recognized as the commonest cardiovascular problems in most of the advanced countries and developing countries. Essential hypertension accounts for 90-95% of all cases of hypertension. Hypertension is an emerging health problem in Bangladesh among the cardiovascular diseases. The prevalence rate of hypertension is very high and more than 20% of the adults have hypertension[2] .

The autonomic nervous system (ANS)) plays a fundamental role in the control of arterial blood pressure and heart rate. Essential hypertension is associated with altered autonomic function[1]. Hypertension is characterized by sympathetic overactivity[3] and attenuation of parasympathetic modulation of the heart[4].

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The heart rate variability is a powerful noninvasive tool in the assessment of the cardiac autonomic nerve function[5]. Several studies have identified reduced HRV in essential hypertension[3,6,7,8]. Reduced HRV has been correlated with increased mortality after acute myocardial infraction[9,10].

Among the various HRV measures mean R-R interval, mean heart rate, maximum and minimum R-R ratio, SDNN and RMSSD usually used as marker for cardiac vagal activity[11]. Essential hypertension is treated with various antihypertensive drugs which modify the sympatho- parasympathetic balance[3,12]. A prospective randomized trial revealed that losartan significantly increased parasympathetic activity in hypertensiye patients when compared to placebo[13]. Few studies reported losartan inhibit sympathetic activity in hypertensive patients[14,15]. Another study revealed that losartan had no significant effect on HRV in hypertensive patients[16,17]. Few studies revealed that autonomic balance shifted toward the increased vagal activity treated with atenolol in hypertensive patients[17,18]. On the other hand, one study reported that atenolol had no significant effect on HRV[23].

Although several investigators observed the effect of losartan and atenolol on HRV separately but no report compared the effect of losartan and atenolol on HRV in newly diagnosed hypertensive patients. Therefore this study aimed to evaluate HRV in untreated hypertensive patients and compare the effect of losartan and atenolol on HRV.

Methods:

This prospective observational study was carried out to observe the HRV by assessing time domain measures in 120 newly diagnosed hypertensive patients with ranged from 30-55 years in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from July 2012 to June 2013. Age, sex and BMI matched 60 apparently healthy normotensive subjects were also studied as control (group A). Based on treatment, these study subjects were divided into two groups(B1 and B2). Group$B1_a$ included 60 patients received losartan 50mg daily and $B2_a$ included 60 patients received atenolol 50mg daily .They were observed once before the treatment ($B1_a$ & $B2_a$) after3 months medication($B1_b$ & $B2_b$) and after 6 months medication ($B1_c$ & $B2_c$). These patients were selected from the Out Patient Department of Cardiology, BSMMU.

Then the subject was prepared for Autonomic Nerve Function Test. The subject was kept in complete bed rest in supine position for 15-20 minutes in a cool and calm environment. Then all preparations for recording of the Heart rate variability parameters were made by connecting the channels of ECG and a 5 minutes recording was taken in resting position. Time domain parameters of the HRV like Mean heart rate, Mean R-R interval, Max/Min R-R interval, SDNN, RMSSD were measured by polygraph.

Then all the patients were requested to attend the Department of Physiology of BSMMU, again after 3 months and after 6 months of antihypertensive medication, to have the assessment of the above mentioned study variables. For statistical analysis ANOVA, independent sample't' test and paired sample 't' test were performed.

Results:

Table-I

Anthopometric data of all subjects are given in.

Group	Age (years)	BMI (kg/m^2)
A (n=60)	42.04±1.134 (30-35)	23.24±0.243 (18.59-24.77)
B_{1a} (n=60)	41.64±1.165 (30-35)	23.27±0.216 (18.65-24.77)
B_{2a} (n=60)	44.74±1.321 (30-35)	23.01±0.177 (18.37-24.68)
Statistical analysis		
Group	P value	
A vs B_{1a} vs B_{2a} $^{\xi}$	0.296^{ns}	0.850^{ns}
A vs B_{1a} φ	0.806^{ns}	0.912^{ns}
A vs B_{2a} φ	0.124^{ns}	0.656^{ns}
B_{1a} vs B_{2a} $^{\Omega}$	0.533^{ns}	0.748^{ns}

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. ξ = one way anova. φ= independent sample 't' test. Ω=paired sample 't' test.

Group A = Apparently healthy subject (control)

B_1 = Newly diagnosed hypertensive patients before treatment

B_2 = After 3 months treatment with losartan

B_3 = After 3 months treatment with losartan

*** = p<0.001 ns= non significant (p>0.05)

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

* = p<0.05

Mean resting pulse, systolic blood pressure and diastolic blood pressure were significantly higher in group B_{1a} and B_{2a} and this values were significantly decreased in group B_{1b}, B_{1c}, B_{2b} and B_{2c} .(TableII)

Table-II

Baseline measures in different groups (n=120)

Groups	Pulse	systolic blood pressure	Diastolic blood pressure
A	78.15±0.862 (93-70)	126.4±0.603 (120-135)	73.2±0.515 (65-80)
B_{1a}	83.55±0.919 (95-70)	141.6±0.462 (140-155)	91.5±0.295
B_{1b}	76.37±0.767 (90-70)	127.7±0.45 (120-135)	77.4±0.510 (70-85)
B_{1C}	75.33±0.664 (87-65)	127.7±0.449 (120-135)	76.2±0.476 (70-85)
B_{2a}	94.63±0.636 (106-87)	147.6±0.561 (140-155)	92.5±0.333 (90-98)
B_{2b}	70.80±0.517 (77-62)	126.3±0.473 (120-130)	75.9±0.468 (70-80)
B_{2c}	65.17±0.495 (68-52)	125.5±0.449 (120-135)	74.6±0.502 (70-80)

Statistical analysis

Group	P value		
A vs B_{1a} vs B_{2a} vs B_{3a}^{ξ}	0.000***	0.000***	0.000***
A vs B_{1a}^{φ}	0.000***	0.000***	0.000***
A vs B_{2a}^{φ}	0.000***	0.000***	0.000***
B_{1a} vs B_{1b}^{Ω}	0.000***	0.000***	0.000***
B_{1b} vs B_{1c}^{Ω}	0.252ns	0.095ns	0.047*
B_{1a} vs B_{1c}^{Ω}	0.000***	0.000***	0.000***
B_{2a} vs B_{2b}^{Ω}	0.000***	0.000***	0.000***
B_{2b} vs B_{2c}^{Ω}	0.000***	0.038*	0.006**
B_{2a} vs B_{2c}^{Ω}	0.000***	0.000***	0.000***

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. ξ = one way anova. φ= independent sample 't' test. Ω=paired sample 't' test.

SBP = Systolic blood pressure.

DBP =Diastolic blood pressure

Group A = Apparently healthy subject (control)

B_{1a} = Newly diagnosed hypertensive patients before treatment

B_{1b} = After 3 months treatment with losartan

B_{1c} = After 6 months treatment with losartan

B_{2a} = Newly diagnosed hypertensive patients before treatment

B_{2b} = After 3 months treatment with atenolol

B_{2c} = After 6 months treatment with atenolol

*** = p<0.001 ns= non significant (p>0.05)

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

* = p<0.05

Mean values of mean heart rate were significantly higher in group B_{1a} and B_{2a} than that of group A and this values were significantly decreased in group B_{1b} and group B_{1c} in comparison to their baseline value. In addition this value showed no significant difference when compared between groupA and group B_{1c} . Mean heart rate in group B_{2b} and group B_{2c} was significantly lower compared to their baseline value. Mean heart rate in group B_{1c} was significantly lower than that of control group. Mean R-R interval, Max/Min R-R interval were significantly lower in group B_{1a} and B_{2a} than that of group A and this values were significantly increased in group B_{1b}, B_{1c}, B_{2b} and B_{2c} in compared to baseline value. (Table III).

Table-III

Simple time domain measures of HRV in different groups

Groups	Mean heart rate(Beat/ min)	Mean R-R interval (sec.)	Max/min R-R interval
A (n=60)	73.33±0.712 (85-65)	0.753±0.12 (0.91-0.6)	1.75±0.066 (3.17-1.19)
B_{1a} (n=60)	84.85±0.895 (95-70)	0.693±0.014 (1.04-0.571)	1.46±0.041 (3.79-1.12)
B_{1b}	77.75±0.909 (90-65)	0.730±0.10 (1.128-0.619)	1.71±0.64 (4.99-1.104)
B_{1c}	74±0.886 (85-63)	0.748±0.011 (1.135-.551)	1.78±0.057 (12.18-.789)
B_{2a}	97.33±0.864 (113-87)	0.624±0.007 (.80-.531)	1.41±0.055 (2.79-1.06)
B_{2b}	73.82±0.543 (84-65)	0.760±0.012 (2.39-.562)	1.81±0.070 (4.26-1.16)
B_{2c}	61.8±0.556 (69-52)	0.923±0.019 (2.34-0.658)	1.93±0.071 (2.88-1.12)

Statistical analysis

Group	PValue		
A vs B_{1a}^{φ}	0.000***	0.001***	0.000***
A vs B_{1b}^{φ}	0.000	0.122ns	0.714ns
A vs B_{1c}^{φ}	0.243ns	0.747ns	0.694ns
B_{1a} vs B_{1b}^{Ω}	0.000	0.024*	0.002**
B_{1b} vs B_{1c}^{Ω}	0.008	0.239	0.411ns
B_{1a} vs B_{1c}^{Ω}	0.000***	0.001***	0.000***
A vs B_{2a}^{φ}	0.000***	0.001***	0.000***
A vs B_{2b}^{φ}	0.591ns	0.651ns	0.481ns
A vs B_{2c}^{φ}	0.000***	0.001***	0.056ns
B_{2a} vs B_{2b}^{Ω}	0.000***	0.001***	0.000***
B_{2b} vs B_{2c}^{Ω}	0.000***	0.001***	0.190ns
B_{2a} vs B_{2c}^{Ω}	0.000***	0.001***	0.000***

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. φ= independent sample 't' test. Ω=paired sample 't' test.

R-R = interval between successive QRS complex(sec)

Max = maximum

Min =minimum

Group A = Apparently healthy subject (control)

B_{1a} = Newly diagnosed hypertensive patients before treatment

B_{1b} = After 3 months treatment with losartan

B_{1c} = After 6 months treatment with losartan

B_{2a} = Newly diagnosed hypertensive patients before treatment

B_{2b} = After 3 months treatment with atenolol

B_{2c} = After 6 months treatment with atenolol

*** = p<0.001 ns= non significant (p>0.05)

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

* = p<0.05

The mean values of SDNN, RMSSD were significantly lower in group B_{1a} and B_{2a} than that of group A and this values were significantly increased in group B_{1b}, B_{1c}, B_{2b} and B_{2c} than that of their baseline. But these values showed no statistically significant difference between group A and group B1c. (Table IV).

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 (99.8-50.09)	32.69±0.89 (41.89-17.99)
B_{1a} (n=60)	40.63±2.37 (102.8-15.11)	24.57±0.521 (32.99-18.76)
B_{1b}	54.40±2.39 (100.09-26.15)	26.98±0.392 (34.-22)
B_{1c}	71.42±2.53 (108.1-31.09)	30.59±.414 (45.31-23.8)
B_{2a}	27.05±1.94 (81-10.98)	22.43±.194 (25.6-19.9)
B_{2b}	51.3±2.57 (108-18.5)	24.86±.291 (28.7-21.3)
B_{2c}	81.68±3.67	31.21±.371

Statistical analysis

Group	P value	
A vs B_1 $^{\varphi}$	0.000***	0.000***
A vs B_2 $^{\varphi}$	0.000***	0.000***
A vs B_3 $^{\varphi}$	0.036	0.035
B_{1a} vs B_{1b} $^{\Omega}$	0.000***	0.001
B_{1b} vs B_{1c} $^{\Omega}$	0.000***	0.008
B_{1a} vs B_{1c} $^{\Omega}$	0.000***	0.000***
A vs B_{2a} $^{\varphi}$	0.000***	0.000***
A vs B_{2b} $^{\varphi}$	0.000***	0.000***
A vs B_{2c} $^{\varphi}$	0.40 Ins	0.000***
B_{2a} vs B_{2b} $^{\Omega}$	0.000***	0.000***
B_{2b} vs B_{2c} $^{\Omega}$	0.000***	0.000***
B_{2a} vs B_{2c} $^{\Omega}$	0.000***	0.000***

Data were expressed as mean ± SE, figures in parenthesis indicate ranges. φ= independent sample 't' test. Ω=paired sample 't' test.

SDNN = Standard deviation of N-N interval

RMSSD = Square root of mean squared differenceso between adjacent NN intervals.

Group A = Apparently healthy subject (control)

B_{1a} = Newly diagnosed hypertensive patients before treatment

B_{1b} = After 3 months treatment with losartan

B_{1c} = After 3 months treatment with losartan

B_{2a} = Newly diagnosed hypertensive patients before treatment

B_{2b} = After 3 months treatment with atenolol

B_{2c} = After 3 months treatment with atenolol

*** = $p<0.001$ ns= non significant ($p>0.05$)

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

* = $p<0.05$

Discussion:

In the present study, values of the HRV parameters in healthy normotensive group were almost similar to other investigators[5,19].

In this study, the mean resting pulse rate, mean heart rate, resting systolic and diastolic blood pressure were found significantly higher in newly diagnosed hypertensive patients than that of healthy normotensive groups. These values were found significantly lower after 6 months treatment compared to their values after 3 months treatment. Again these values were found close to the values in normotensive subjects. Similar type of findings were also reported by the various investigators from different countries [19,20 ,24]. Again the mean heart rate was found significantly lower in atenolol treated patients than those of controls.

Again in this study significantly lower the mean R-R interval , Max/Min R-R interval, SDNN and RMSSD in untreated hypertensive patients indicate lower cardiac vagal modulation .Result of these parameters after 3 months and 6 months treatment with both losartan and atenolol group showed significant improvement. Again when the effect of this two drugs on cardiac autonomic nerve function was compared, the result of the study showed atenolol is more effective than losartan in increasing the cardiac vagal activity supported by the significantly higher value of mean R-R interval, SDNN, RMSSD and lower value of mean heart rate in atenolol treated hypertensive subjects. These values were found significantly higher after 6 months treatment compared to their values after 3 months treatment[15.17,21]. Again these values were found close to the values in normotensive subjects. Moreover this value was significantly higher in atenolol treated group than that of losartan treated group. Similar findings in these two parameters were also reported by the various investigators of different countries[1,15,17, 18, 22,24].

Investigators suggested that essential hypertension is associated with altered autonomic regulation, which is supported by reduced HRV, sympathetic over activity and low Baroreflex sensitivity (BRS)[5,17,20,21].

Different investigators suggested various mechanisms for the improvement of HRV in hypertensive patients after treatment with losartan and atenolol. It has been suggested that blocking the type-I receptor (AT_1) of Angiotensin II by losartan would release the baroreceptor from the suppresor effect of high level of Angiotensin II leading to increase BRS which in turn bring the sympathovagal balance back towards normal.The benefit of blocking the type-I receptor (AT_1) of Angiotensin II by losartan is also derived from its ability to increase NO production from vascular endothelium and neuron which in turn facilitate the regulation of BRS and HRV in losartan treated hypertensive group [25]. Furthermore, NO has been demonstrated to augment cardiac vagal control in human suggesting beneficial effect on BRS and HRV[26].

Beta blocker lower blood pressure predominently by inhibiting beta-1 adrenergic receptors, cardiac contractility and heart rate which in turn facilitates vagal activity. Renin release and angiotensin II are also inhibited by this mechanisms. Additionally, beta blocker alter BRS, and increase prostacyclin biosynthesis, thereby facilitating vasodilatation[27].

The exact mechanisms involved for the decreased HRV and BRS in hypertension and improvement after treatment with losartan and atenolol in hypertensive groups of present study can not be elucidated from this type of study. However, it is assumed that all the above mentioned mechanisms may influence the degree of deterioration of these variables in hypertension patients and improvement after treatment with losatan and atenolol. From the result though the improvement of cardiac autonomic nerve function was marked after 3 months of treatmebt but data after 6 months of treatment showed further improvement. This is suggestive of positive relation and duration of treatment with antihypertenstve drugs with improvement of HRV.

Conclusion:

Impairment of cardiac autonomic nervous activity occurs in newly diagnosed hypertensive patients which is improved by both losartan and atenolol and in particular atenolol was found more effective. The rate of improvement of impaired cardiac autonomic function releated to their duration of treatment.

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