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Evaluation of Effects of Losartan and Nebivolol on Oxidative Stress Parameters in Dialysis Patients

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Abstract

Aim: Oxidative Stress (OS) is a well-defined risk factor of Atherosclerosis (AS) in dialysis patients. We aimed to compare the effects of losartan and nebivolol on the level of OS parameters such as Total Antioxidant Capacity (TAC), erythrocyte Superoxide Dismutase (SOD) and Total Oxidant Status (TOS) in patients receiving Hemodialysis (HD) or Peritoneal Dialysis (PD).

Material and Method: Eighty patients on PD or HD for at least 6 months without antihypertensive medication and 30 years age and gender matched healthy volunteers were selected in this study. The patients were and only assigned into two groups; losartan (group I) and nebivolol (group II). Plasma levels of TAC, SOD and TOS were analyzed. Oxidative Stress Index (OSI) was calculated based on the ratio of TOS level to TAC level (TOS/TAC). Subsequent to initial evaluation of patients and healthy subjects, losartan 50 mg to 100 mg and nebivolol 5 mg were initiated.

Findings: Statistically significant differences were observed between patients and control group in terms of pro-oxidants (TOS and OSI), and antioxidants (TAC and erythrocyte SOD) ($p=0.002$, $p=0.005$, $p=0.002$, $p<0.001$; respectively). We detected significant increase in TAC levels ($p<0.001$), decrease in TOS levels, and OSI values ($p=0.019$, and $p<0.001$; respectively), and nonsignificant change in SOD levels ($p=0.087$) in patients receiving nebivolol therapy. At the final evaluation, there was no significant difference between losartan and nebivolol groups in terms of blood pressure or TAC, TOS, OSI, and SOD levels ($p=0.574$, $p=0.696$, $p=0.586$ and $p=0.534$; respectively).

Conclusion: Although the positive effect of nebivolol treatment was more evident, we failed to demonstrate a significant difference between losartan and nebivolol treatments with regard to OS parameters including TAC, TOS, OSI and erythrocyte SOD.

Keywords: Hemodialysis; Peritoneal dialysis; Losartan; Nebivolol; Oxidative stress

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Introduction

Patients with End Stage Renal Disease (ESRD) are associated with 3.5 times to 50 times increased risk of Atherosclerosis (AS), and AS related cardiovascular disorders [1,2]. Cardiovascular risk factors including hypertension, dyslipidemia, Left Ventricular Hypertrophy (LVH), heart failure and physical inactivity are frequently seen in patients on Renal Replacement Therapy (RRT), particularly depending on the fact that this population consist of patients at advanced age with diabetic and vascular disorders [3]. ESRD is, also, associated with non-traditional risk factors that are specific to uremia including chronic hypervolemia, anemia, calcium-phosphorus imbalance disorders, hyperhomocysteinemia and enhanced OS due to micro inflammatory state [3,4].

Beside well document ted relation between OS and aging, diabetes, uremia, cardiovascular diseases, mal nutrition and cancer, it is also associated with development and progression of complications of systemic disorders [4,5]. Pro-oxidant/antioxidant balance changes toward OS in ESRD. Patients with ESRD are exposed to excessive OS due to nature of renal diseases as well as dialysis procedure, dialysate, dialysis membrane, activators of immune system and other pharmacological therapies. The negative effects of OS on the development of AS is well-defined in patients undergoing dialysis [6,7].

Angiotensin Receptor Blockers (ARB) reduces OS *via* inhibition of NADPH oxidase [8], decreasing O_2^- [9], and oxide-LDL [10] and reducing Advanced Glycation End (AGE) products [11]. Nebivolol; a third generation highly selective β blocker, acts by enhancing urinary excretion of 8-iso-PGF2a [12] which is produced by peroxidation of arachidonic acid, decreasing oxidative

inactivation and increasing Nitric Oxide (NO) in endothelium. In the present study, our aim was to evaluate the effects of losartan and nebivolol on OS in patients receiving HD or PD.

Materials and Methods

Patients groups

Eighty patients on PD or HD for at least 6 months without antihypertensive therapy in Dialysis Center of Medical School of Dicle University were enrolled into this study. Exclusion criteria were Diabetes Mellitus (DM) chronic infections and inflammation conditions (such as tuberculosis and rheumatoid arthritis, etc), is chemic heart diseases, congestive heart failure and antihypertensive medication. All patients were informed about treatment, follow-up and complications. Patients were randomly assigned into two groups. Patients in group I and II received losartan (Cozaar® 50 mg to 100 mg tablet, Merck Sharp Dohme, USA) and nebivolol (Vasoxen® 5 mg tablet, İbrahim Ethem Ulagay/Menarini International, Italy); respectively. Follow-up duration was planned to be 6 months. Blood Pressure (BP) of patients were closely monitored.

Control group

Controls were consisting of 30 healthy volunteers that were non-smoker and non-alcoholic employees of Medical School of Dicle University without history of any medication in last 15 days.

Preparation of samples

Blood samples were collected from antecubital vein after 12 h fasting period before dialysis session in HD patients and first change in PD patients. Blood samples were stored in 2 biochemical tubes for analyzing OS and biochemical parameters and in hemogram tubes containing K-EDTA to prepare erythrocyte package for erythrocyte SOD analysis. Samples were centrifuged at room temperature in 3,000 gm for 15 min. Blood samples and erythrocytes were stored at - 80°C until analysis. Full automated calorimetric method which is developed by Erel was used to analyze Total Antioxidant Capacity (TAC) and Total Oxidant Status (TOS) [13,14]. Oxidative Stress Index (OSI) was measured by ratio of Total Oxidant Level to Total Antioxidant Capacity (TOL/TAC) [15]. Erythrocyte Superoxide Dismutase (SOD) activity was spectrophotometrically analyzed with enzymatic method by using commercially available kits (Randox Lab. Ransod® (Kat. No. SD 125).

Biochemical parameters including serum glucose, urea, creatinine, cholesterol, triglycerides, calcium and phosphorus were analyzed by Aeroset/C8000 autoanalyzer (Abbott Diagnostics, Abbott Park, Chicago, IL, USA); Serum levels of C-Reactive Protein (CRP), electrochemiluminescence method on Roche Elecsys 2010 immunoassay analyzer (Roche Diagnostics Corporation, Indianapolis, IN, USA), iPTH; two-site chemiluminescent enzyme-labeled immunometric method on IMMULITE 2000 (Diagnostic Products Corporation, Los Angeles, CA, USA). Leucocyte count and hemoglobin levels were examined by Cell-dyn 3700 (Abbott Diagnostics, Chicago, IL, USA).

This study was approved by the non-interventional clinical researches Ethics Committee of Medical School of Dicle University.

Statistical analysis

SPSS 13.0 PC (SPSS package 13.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Independent variables were analyzed by student's t-test. Wilcoxon Signed Rank test was used for assessment of dependent variables. The relation of variables was evaluated by Pearson's correlation analysis. Data were expressed as mean ± SD. A p value <0.05 was considered significant.

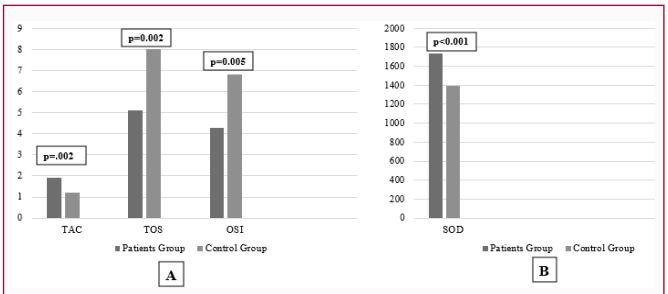

Figure 1: Comparison of pro-oxidant and antioxidant parameters of patients and controls. A) TAC (Total Antioxidant Capacity - µmol Trolox Eqv./L), TOS (Total Oxidant Status - µmol H_2O_2 Eqv./L), and OSI (Oxidative Stress Index). B) SOD (Erythrocyte Superoxide Dismutase - U/gHb).

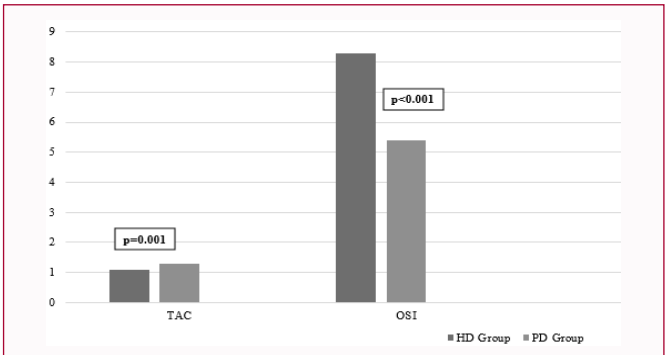

Figure 2: Comparison of pro-oxidant and antioxidant parameters of hemo dialysis and peritoneal dialysis groups.
HD: Hemodialysis; PD: Peritoneal Dialysis; TAC: Total Antioxidant Capacity (µmol Trolox Eqv./L); OSI: Oxidative Stress Index

Findings

A total of 110 participants, losartan group (n=40), nebivolol group (n=40) and control group (n=30) were enrolled. Five patients in group I (four patients transferred to another dialysis center and 1 patient underwent to transplantation) and 4 patients in group II (two patients transferred to another dialysis center and 2 patients died) were excluded. Thirty-five patients in group I and 36 patients in group II were scheduled until last visit. Fifteen patients were receiving HD and 20 patients were on PD.

Nineteen patients were receiving HD and 17 patients were on PD in group II. Table 1 summarize demographic, clinical and laboratory characteristics of patients and controls.

There was a statistically significant difference between patients and control group with regard to prooxidants like TOS and OSI, and antioxidants like TAC and erythrocyte SOD (p=0.002, p=0.005, p=0.002 and p<0.001; respectively). Comparison of pro-oxidant and antioxidant parameters of patients and controls were shown in Table 2 and Figure 1. When dialysis modality of patients were taken into consideration, no significant difference was observed between groups in terms of TOS (p=0.253) and SOD (p=0.568) however TAC (p=0.001) and OSI (p<0.001) levels were significantly better in PD group as shown in Table 3 and Figure 2.

At the initial evaluation, differences of demographic, clinical and laboratory data of group I and II were non-significant. Table 4 demonstrates demographic, clinical and laboratory data of groups at

Table 1: Laboratory characteristics of patients and controls.

Parameters	Patients group (n=71)	Control group (n=30)	p
Age (years)	40.9 ± 14.0	38.0 ± 10.5	0.389
Gender (M/F)	34/37	14/16	0.983
BMI (kg/m^2)	21.9 ± 4.3	24.3 ± 3.7	0.025
SBP (mmHg)	136.6 ± 28.2	116.6 ± 12.3	0.002
DBP (mmHg)	83.9 ± 13.6	77.1 ± 9.0	0.035
Glucose (mg/dl)	104.3 ± 49.9	93.1 ± 11.8	0.314
CaxP (mg^2/dl^2)	55.2 ± 19.2	34.9 ± 4.9	<0.001
iPTH (pg/ml)	382.6 ± 386.9	49.5 ± 19.1	<0.001
Hgb (g/dl)	10.4 ± 1.7	14.4 ± 1.2	<0.001
Albumin (g/dl)	3.3 ± 0.5	4.3 ± 0.2	<0.001
CRP (mg/dl)	13.5 ± 29.4	3.4 ± 0.4	0.119
Total cholesterol (mg/dl)	185.6 ± 56.6	171.7 ± 36.7	0.292
Triglyceride (mg/dl)	185.8 ± 139.4	140.1 ± 97.1	0.164
LDL-C (mg/dl)	111.9 ± 38.1	97.9 ± 29.2	0.126
HDL-C (mg/dl)	38.6 ± 12.0	45.9 ± 10.4	0.014

Table 2: Pro-oxidant and antioxidant parameters of patients and controls.

Parameters	Patients group (n=71)	Control group (n=30)	p
TAC (µmol Trolox Eqv./L)	1.9 ± 1.8	1.2 ± 0.3	0.002
TOS (µmol H_2O_2 Eqv./L)	5.1 ± 1.8	8.0 ± 4.7	0.002
OSI	4.3 ± 2.5	6.8 ± 3.5	0.005
SOD (U/gHb)	1730.4 ± 228.4	1391.6 ± 252.9	<0.001

TAC: Total Antioxidant Capacity; TOS: Total Oxidant Status; OSI: Oxidative Stress Index; SOD: Erythrocyte Superoxide Dismutase

Table 3: Pro-oxidant and antioxidant parameters according to dialysis modality.

Parameters	HD Group (n=34)	PD Group (n=37)	p
TAC (µmol Trolox Eqv./L)	1.1 ± 0.3	1.3 ± 0.3	0.001
TOS (µmol H_2O_2 Eqv./L)	8.7 ± 5.5	7.4 ± 3.8	0.253
OSI	8.3 ± 3.9	5.4 ± 2.5	<0.001
SOD (U/gHb)	1409.7 ± 262.5	1375.1 ± 246.2	0.568

TAC: Total Antioxidant Capacity; TOS: Total Oxidant Status; OSI: Oxidative Stress Index; SOD: Erythrocyte Superoxide Dismutase

the initial visit.

Reduction of mean BP levels were significant in both groups when compared to initial BP examination (p<0.001 and p<0.001; respectively) however, it was non-significant between group I and II (p=0.699 and p=0.737 for systolic and diastolic BP; respectively). Patients in losartan group exhibited significant increase in TAC (p<0.001), decrease in OSI (p<0.001), and no significant change in TOS and SOD levels (p=0.272 and p=0.404; respectively). On the other hand, TAC levels were significantly increased (p<0.001), TOS and OSI levels were significantly decreased (p=0.019 and p<0.001; respectively) in nebivolol group. No significant change was observed in SOD levels (p=0.087).

There was no significant change in BP, TAC, TOS, OSI and SOD levels between pretreatment and post treatment period (p=0.574, p=0.696, p=0.586 and p=0.534; respectively). The results were shown in Table 5.

Table 4: Demographic, clinical and laboratory characteristics of patients at initial examination.

Parameters	Losartan group (n=35)	Nebivolol group (n=36)	p
Age (years)	39.9 ± 12.7	41.9 ± 15.3	0.55
Gender (M/F)	14/21	20/16	0.7
Duration of dialysis (months)	45.9 ± 41.5	42.0 ± 43.3	0.7
Follow-up duration (day)	196.3 ± 33.7	198.5 ± 15.6	0.73
BMI (kg/m^2)	21.9 ± 4.0	21.9 ± 4.6	0.97
SBP (mmHg)	139.7 ± 34.1	133.6 ± 20.9	0.37
DBP (mmHg)	86.5 ± 14.1	81.3 ± 12.9	0.11
Glucose (mg/dl)	105.8 ± 50.8	102.9 ± 49.8	0.81
CaxP (mg^2/dl^2)	54.0 ± 8.8	56.4 ± 19.8	0.61
iPTH (pg/ml)	349.8 ± 291.2	414.5 ± 463.6	0.49
Hgb (g/dl)	10.5 ± 1.9	10.3 ± 1.4	0.53
CRP (mg/dl)	8.4 ± 9.3	18.4 ± 39.9	0.15
Total cholesterol (mg/dl)	185.9 ± 67.3	185.3 ± 44.3	0.97
Triglyceride (mg/dl)	195.9 ± 79.5	175.9 ± 85.7	0.55
LDL-C (mg/dl)	107.9 ± 27.2	115.7 ± 36.1	0.39
HDL-C (mg/dl)	40.0 ± 13.9	37.2 ± 9.7	0.33

Discussion

Cardiovascular Diseases (CVD) are the leading cause of mortality in ESRD because of the cumulative effect of multiple risk factors. Beside well-known risk factors such as hypertension, diabetes and nicotine exposure, several other factors that are specific to uremia including chronic hypervolemia, anemia, calcium-phosphorus metabolism disorders, hyperhomocysteinemia, increased a symmetric dimethylarginine (ADMA), and microinflammation related to enhanced OS are also involved in the pathogenesis of CVD [6-8]. There is a dual relation between OS and inflammation in uremic patients [7,8]. Decreasing OS under acceptable levels does not warrant preventing development of CVD in ESRD patients. Also, decreasing cardiovascular risk factors, augmenting life quality and improving survival play crucial role.

OS that leads to pro-oxidant/antioxidant imbalance and tissue damage has a vital importance in development, progression and complications of several disorders [16]. Despite controversial reports [17], it is a disorder characterized by imbalance of pro-oxidants and antioxidants which also associated with complications of AS and β_2 macroglobulin amyloidosis [18]. OS may be reduced by erythropoietin therapy [19], vitamin supplementation [20,21], and use of different dialysis membranes which raise the expectation of positive results [22]. To the best of our knowledge, there is no other study that compares ARB's and new generation beta blockers that mediate by NO. Shimada et al. [23] showed that telmisartan may decrease OS by leading to significant reduction of oxide albumin. Biasioli et al. [22] determined that OS is already increased in dialysis patients which additionally increase by use of cuprophane membrane. In the present study, total OS was increased in patients with ESRD as compared to healthy controls. TOS and OSI levels were significantly higher (p=0.002 and p=0.005; respectively) and TAC and SOD levels were significantly lower in dialysis patients (p=0.002 and p=0.001; respectively) than controls. This result suggests not only increased pro-oxidants but also inadequacy of antioxidant defense mechanism

Table 5: Blood pressure level, pro-oxidants and antioxidants parameters of pretreatment and posttreatment period.

Parameters	Losartan group (n=35)		Nebivolol group (n=36)		P[1]
	Pre treatment period	Post treatment period	Pre treatment period	Post treatment period	
SBP[a]	139.7 ± 34.1	115.2 ± 26.4	133.6 ± 20.9	117.2 ± 16.3	0.7
DBP[a]	86.5 ± 26.4	73.4 ± 12.1	81.3 ± 12.9	72.5 ± 11.0	0.74
TAC[b]	1.2 ± 0.4	1.5 ± 0.3	1.2 ± 0.3	1.6 ± 0.2	0.57
TOS[c]	8.2 ± 5.6	6.5 ± 1.9	7.9 ± 3.5	6.3 ± 0.9	0.7
OSI	6.7 ± 3.1	4.0 ± .8	6.9 ± 3.8	4.0 ± 0.9	0.59
SOD[d]	1388.9 ± 247.9	1423.7 ± 252.6	1394.3 ± 261.1	1459.0 ± 222.8	0.53

involved in the pathogenesis of OS in patients with ESRD. When patients in three groups were classified according to dialysis modality, we observed no significant difference between patients on HD and PD in terms of TOS and SOD (p=0.253 and p=0.568; respectively) however, TAC and OSI levels were significantly better in PD group (p=0.001 and p<0.001; respectively). In accordance with the results of the study by Pawlak et al. [24], we determined that antioxidant effect was better in PD group which probably suggests favorable impact of PD *via* suppression of immune system due to extra corporeal circulation and use of biocompatible membrane [24,25].

Beneficial antioxidant effects of ACEI's and ARB's were shown in both diabetic and non-diabetic population. In experimental animal models, angiotensin II has been related with increased ROS by stimulating NADPH oxidase [26]. It was supported by human models [27]. Berry et al. demonstrated that ACEI and ARB the rapies may diminish O_2 levels in patients with coronary artery diseases [9]. Onozato et al. [8] showed that ACEI's inhibit renal NADPH oxidase and reduce proteinuria in rats with diabetic nephropathy. Fan et al. [11] demonstrated that candesartan diminish AGE formation and OS. In our study, we observed decrease of pro-oxidants and increase in antioxidants in losartan group. Among pro-oxidants, OSI decreased from 4.1 ± 0.8 to 3.6 ± 0.5 (p=0.004). In addition, although it was non-significant, TOS levels decreased from 8.2 µmol H_2O_2 Eqv./L ± 5.6 µmol H_2O_2 Eqv./L to 6.5 µmol H_2O_2 Eqv./L ± 1.9 µmol H_2O_2 Eqv./L (p=0.272). Among antioxidants, TAC levels decreased from 1.5 µmol Trolox Eqv./L ± 0.3 µmol Trolox Eqv./L to 1.2 µmol Trolox Eqv./L ± 0.4 µmol Trolox Eqv./L (p<0.001) and SOD levels decreased from 1388.9 U/gHb ± 247.9 U/gHb to 1423.7 U/gHb ± 252.6 (p=0.404). Inconsistent with previous reports [28], increase of pro-oxidants and decrease of antioxidants exhibit favourable effect of losartan on OS in ESRD patients on dialysis.

The effect of nebivolol on OS is well-defined by Troost et al. [12], Gupta et al. [29] and Fratta Pasini et al. [30]. In our study, when pretreatment and post treatment levels of pro-oxidants were compared, it was showed that OSI and TOS levels were decreased from 6.9 ± 3.8 to 4.0 ± 0.9 (p<0.001) and from 7.9 µmol H_2O_2 Eqv./L ± 3.5 µmol H_2O_2 Eqv./L to 6.3 µmol H_2O_2 Eqv./L ± 0.9 µmol H_2O_2 Eqv./L (p=0.019); respectively. Among antioxidants, TAC and SOD levels increased from 1.0 µmol Trolox Eqv./L ± 0.3 µmol Trolox Eqv./L to 1.6 µmol Trolox Eqv./L ± 0.2 µmol Trolox Eqv./L (p<0.001) and 1394.3 U/gHb ± 261.1 U/gHb to 1459.0 U/gHb ± 222.8 U/gHb (p=0.087), respectively. The positive changes in all parameters were in accordance with the literature [31].

The goal to reach to target BP was achieved in both losartan and nebivolol groups. Although BP levels in both groups were slightly elevated, the mean systolic and diastolic BP decreased from 136.6 ± 28.2 mmHg and 83.99 ± 13.6 mmHg to 116.2 ± 21.7 mmHg and 72.9 ± 11.5 mmHg; respectively (p<0.001 for both). When groups were analyzed on one's own, significant decrease in BP were achieved in both groups (p<0.001).

A limited number of sole and comparative studies exist to develop newer therapeutic approachments against OS in dialysis patients. Celik et al. [32] compared the effects of nebivolol and metoprolol on OS, and observed that efficacy of nebivolol was apparently better. We determined no significant difference between losartan and nebivolol groups with regard to age, gender, dialysis duration, follow-up period, BMI, URR, systolic and diastolic BP. There was no significant difference between groups in terms of pro-oxidants [TOS (p=0.574) and OSİ (p=0.586)] and anti-oxidants [TAK (p=0.915) and SOD (p=0.534),]. These results suggest that effects of β blockers band ARB on OS in ESRD patients were similar.

Conclusion

OS is enhanced in ESRD patients on dialysis when compared to normal population. The effects of losartan and nebivolol on TAC, TOS, OSI and erythrocyte SOD levels were similar. However, positive effect of nebivolol on OSI was more apparent as groups were evaluated on one's own.

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