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Research Article

The Effect of Massage and Biochemical Oxidative Stress Determinants in Hemodialysis Patients with Restless Leg Syndrome in Turkish People

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Abstract:

There is limited information about the etiological factors, treatment methods, and the relationship between oxidative stress and antioxidants of restless legs syndrome (RLS) in patients with chronic kidney disease (CKD). This continues to be a significant problem in patients with RLS and CKD. Therefore, it may be useful to target the hypothesis that 'RLS disease may be associated with underlying inflammation and the oxidative stress it creates'. To evaluate the effect of massage and the relationship between biochemical oxidative stress markers and the disease in hemodialysis patients with restless legs syndrome. Eligible patients with CKD stage 4 (CKD 4), pre-dialysis stage 5 (CKD-5ND) and hemodialysis-dependent stage 5 (CKD-5D) patients were enrolled from local dialysis units and kidney clinics. The International RLS Study Group rating scale was used to diagnose RLS and measure its severity. Blood samples were taken before and after treatment and the levels of some oxidative stress and antioxidant parameters were examined. In the intra-group comparison of experimental and control; In the experimental group, after the massage, RLS, TAC and TOC values decreased significantly compared to before the massage, while NO and PON values increased significantly.

1. Introduction

Chronic kidney failure is one of the most common health problems in our country and around the world. Hemodialysis is one of the treatment methods for the disease. However, it is stated that acute and chronic complications may occur during hemodialysis [1,2]. One of these complications is restless legs syndrome (RLS). According to the definition of the International Working Group, the disease, whose etiopathogenesis is not clearly known, is a common neurological sensorimotor disease that may vary depending on genetic, medical and environmental factors, causes a feeling of uneasiness in the legs that is difficult to describe and is initiated by the desire to move, causing pain and discomfort [2,3]. This syndrome is seen in up to 80% of patients receiving long-term dialysis treatment and is important because it is associated with an increased risk of death. There are various study results regarding the prevalence of late-stage RLS, and it is reported to be 15.8% in Iran, 22% in Japan, 25.3% in Taiwan, 26.6% in Greece and 52.6% in Brazil [2, 4-7].Many treatments are applied to prevent this unwanted and uncomfortable discomfort in the legs. Massage is one of these treatment methods. Non-

pharmacological treatment methods include regular daily exercise, running, stretching, hot water bath, cold water bath, acupuncture, massaging the affected muscles, and relaxation exercises (biofeedback or yoga). It is also stated to the patient that avoiding caffeine, alcohol and tobacco consumption will help reduce symptoms [8]. Vibration, one of the non-pharmacological methods, causes an increase in the patient's body temperature, which in turn leads to an increase in oxygen release from myoglobin and hemoglobin, an increase in muscle blood flow, an increase in the sensitivity of neural receptors, an increase in nerve velocity and a decrease in muscle viscosity [9]. These effects are expected to be related to oxidative stress and the antioxidant system. Oxidative stress, autonomic dysfunction and vascular pathologies, which are thought to be related to RLS, are frequently seen in RLS patients; Studies have reported that there is a constant oxidative stress in hemodialysis patients [10]. Increased free oxygen radicals (SOR) in these patients can cause endothelial dysfunction with atheromatous plaque formation by causing lipoprotein modification and leukocyte stimulation [11]. Today, it has been shown that SOR can play a role in the pathogenesis of many diseases [12-14].

There are very few studies in the literature showing that oxidative stress plays a role in the pathogenesis of restless legs syndrome in hemodialysis patients [15-19]. In this context, this study is important to reveal the effect of massage on hemodialysis patients with restless legs syndrome and their relationship with biochemical oxidative stress markers, as well as TOC, TAC, OSI, NO and PON values in the blood, in terms of revealing their relationship with the disease and massage. Thus, it aims to contribute to the literature by revealing the effective factors in the treatment of RLS in a different dimension and determining new supportive treatments.

2. Material and Methods

Hypotheses of the Research

H0a: Individuals with restless legs syndrome receiving hemodialysis treatment; During the second hour of hemodialysis, both calf muscles were massaged for 10 minutes, three times a week for one month.

H1a: Individuals with restless legs syndrome receiving hemodialysis treatment; During the second hour of hemodialysis, both calf muscles were massaged for 10 minutes, three times a week for one month.

Biochemical Tests:

Blood samples taken from the patients will be placed in 10 ml EDTA tubes and brought to the laboratory in an ice bag. Then, it will be centrifuged at 3000 rpm for 10 minutes and the remaining plasma part will be transferred to capped polypropylene tubes. These taken plasmas could be stored in deep freeze at –20˚C until the day of analysis.To this study; Blood samples were taken before and after treatment from 42 female patients over the age of 40 who were diagnosed with knee OA at Başkent University Ankara Hospital. Total antioxidant level (TAC): It will be determined by the automatic measurement method based on the principle that the characteristic color formed by the 2,2'azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid) (ABTS) radical is revealed by the antioxidants in the sample added to the medium [20]. Results will be given in mmol Trolox eqivalen/L. Total oxidant level (TOC): will be determined by automatic measurement method [21]. The oxidants in the sample have the task of converting the ferrous ion complex into ferric ion. The ferric ion (Fe^{3+}), formed by the oxidation of iron (Fe^{2+}) to its more stable form (Fe^2O_3), creates color with xylenol orange in an acidic environment. The intensity of the color measured spectrophotometrically is related to the total amount of oxidant molecules present in the sample. The measurement is calibrated with hydrogen peroxide (H_2O_2) and the results will be given as micromolar H_2O_2 equivalent per liter (μmol H_2O_2 equiv./L) [22]. Nitric oxide (NO): Serum nitric oxide concentration will be measured in a spectrophotometer (PowerWawe XS, BioTek, USA) according to the method [23]. Serum samples will be deproteinized with 10% zinc sulfate. In this method, nitrate was converted to nitrite with Vanadium (III) chloride. It is based on the measurement of the complex diazonium compound as a result of the reaction of nitrite and sulfanilamide N-(1-Naphthy) ethylene diamine dihydrochloride in an acidic environment. Measurement of paraoxonase (PON1) activity: Measurement of PON1 activity was performed by Eckerson et al. [24]. PON1 activity was determined by measuring the absorbance of the colored product of 4-nitrophenol, formed as a result of the enzymatic hydrolysis of paraoxon (Sigma Co, London, UK) used as a substrate, on a spectrophotometer at 25 °C and 412 nanometers. For paraoxonase activity, the enzyme activity of the enzyme in 1 ml of serum that converts 1 nmol of paraoxon to 4-nitrophenol in 1 minute was defined as the unit and the results were given as U/L [24]. Oxidative Stress Index (OSI): OSI was accepted as the percentage of the ratio of TOC level to TAS level. For calculation, unit results of TAC were changed to mmol/L. OSI was calculated according to the following formula: OSI (Arbitrary

Unit): TOS (μmol H_2O_2 equiv./L) / TAC (mmol Trolox eqiv./L) [25].

Statistical Analysis

Data were evaluated with SPSS (Statistical Package for the Social Sciences) for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Frequency, percentage, mean and standard deviation (SD) were used to present categorical and continuous variables. In the intra-group comparison, the Shapiro Wilk test was applied by taking the difference between the measurements within the experimental and control groups. Paired sample t test was applied for those with normal distribution and Wilcoxon test for those without normal distribution. For comparison between groups, Shapiro Wilk test was applied to continuous data, independent sample t test was applied for those with normal distribution, and Mann Whitney U test was applied for those with non-normal distribution. The significance level was accepted as $p<0.05$.

Ethics statement

Approval was granted from the Ethics Committee before collecting the data (dated 28 September 2022, and numbered E-94603339-604 KA22/362). This study is also listed in the Clinical Trials Registry (code number: NCT05787080) on 2023.24.03. The study was conducted in accordance with the Helsinki Declaration of 1975. For the research, permission was obtained from the dialysis center where the study would be conducted. Written informed consent was obtained from the participants after a detailed explanation was given to the participants about the study.

Results

Some descriptive characteristics of the patients are given in table 1. The experimental group consists of 20 patients and the control group consists of 22 patients. The average age of the experimental group is 60.70±16.89, while the average age of the control group is 58.29±17.03. The CKD diagnosis period of the patients in the experimental group was 12.55±11.73 years, and that of the control group was 10.33±6.37 years. When examined in terms of duration of dialysis; It was determined that the patients in the experimental group received dialysis for 5.40±5.57 years, while those in the control group received dialysis for 7.05±5.15 years (Table 1).

Table 1. Some descriptive characteristics of the patients(n=42)

X̄: ortalama; SD: standart sapma; n: sayı.

Characteristics of the patients are given in table 2. It was determined that 72.7% of the patients in the experimental groups were male and the majority were married (63.6%). It was determined that 54.5% of the patients in the experimental groups had a high school education (Table 2). The patients in the control group; It was found that the majority of them were female (65.0%) and their marital status was married (65.0%). It was determined that 40.0% of the patients in the control group had a higher education level.

In the comparison between experimental and control groups; TAC value after massage is 2.30±0.29, respectively; 2.17±0.19, TOC value is 8.56±0.94, respectively; 10.55±0.88, OSI value 0.38±0.09 respectively; 0.49±0.07, NO value 6.25±0.66 respectively; 7.03±0.87, PON value 158.36±25.67 respectively; It was found to be 137.82±26.66.

Table 1. *Descriptive characteristics of the patients(n=42)*

Features	**Experimental group (n=22)**	**Control grup (n=20)**
	X̄±SD	**X̄±SD**
Age	60.05±17.18	59.65±16.25
Diagnosis time	12.05±11.31	10.60±6.41
Dialisis receiving time	5.27±5.32	7.35±5.09

Features		**Experimental group (n=22)**		**Control grup (n=20)**	
		n	**%**	**n**	**%**
	Gender				
Famale		6	27.3	13	65.0
Male		16	72.7	7	35.0
	Marital status				
Married		14	63.6	13	65.0
Single		8	36.4	7	35.0
	Educational background				
Litarete		1	4.5	1	5.0
Firstread		3	13.6	1	5.0
Middle school		0	0	3	15.0
High school		6	27.3	4	20.0
College		12	54.5	8	40.0
Not litatete		0	0	3	15.0

n: sayı.

In the comparison between experimental and control groups; TAC value after massage is 2.30±0.29, respectively; 2.17±0.19, TOC value is 8.56±0.94, respectively; 10.55±0.88, OSI value 0.38±0.09

respectively; 0.49±0.07, NO value 6.25±0.66 respectively; 7.03±0.87, PON value 158.36±25.67 respectively; It was found to be 137.82±26.66.

Table23. *Comparison of some parameters of the patients within and between groups(n=42)*

Features	**Experimental group (n=22)**	**Control grup (n=20)**	**Test P value**
	X̄±SD	**X̄±SD**	
TAC Before	2.58±0.31	2.64±0.20	U=204.50; p=0.69***
TAC After	2.30±0.29	2.17±0.19	U=162.50; p=0.14***
Test P value	Z=-4.14; **p=0.00***	t=27.92; **p=0.00****	
TOS Before	9.51±1.03	9.23±0.78	U=179.00; p=0.30***
TOC After	8.56±0.94	10.55±0.88	U= 37.00; **p=0.00*****
Test P value	t=26.85; **p=0.00****	Z=-3.92; **p=0.00***	
OSI Before	0.37±0.08	0.35±0.05	U=194.00; p=0.51***
OSI After	0.38±0.09	0.49±0.07	t=4.13; **p=0.00******
Test P value	Z=-1.83; p=0.06*	t=-22.54; **p=0.00****	
NO Before	5.58±0.60	5.63±0.77	t=0.24; p=0.81******
NO After	6.25±0.66	7.03±0.87	t=3.22; **p=0.00******
Test P value	Z=-4.10; **p=0.00***	Z=-3.92; **p=0.00***	
PON Before	109.37±21.38	109.43±20.38	t=0.01; p=0.99******
PON After	158.36±25.67	137.82±26.66	t=-2.543; **p=0.01******
Test P value	t=-24.94; **p=0.00****	Z=-3.92; **p=0.00***	

Wilcoxon test was performed; **T test (comparison of measurement values within groups) was performed in dependent groups; ***Mann Whitney U test performed; ** t test in independent groups (comparison of measurement values between groups); X̄: mean; SD: standard deviation; p: significant value.TOC: Total oxidant capacity (μmol H_2O_2 eq/L), TAC: Total antioxidant capacity(nmol Trolox eq/L, NO:μmol/L, PON:U/L, OSI:AU*

Comparing the average scores of the experimental and control groups after the massage; The difference between TOC, OSI, NO averages is statistically significant and lower in the experimental group, while the PON value is significantly higher in the experimental group ($p<0.05$). There was no significant difference in TAC, TOC, OSI, NO and PON between the test and control groups before the massage ($p>0.05$) (Table 2).

In the comparison of experimental and control groups; In the experimental group, after the massage, TAC and TOC values significantly decreased, NO and PON values significantly increased ($p>0.05$). There was no significant difference in OSI value between before and after massage in Deney group ($p>0.05$). It is in the control group; The TAS value of the measurement decreased significantly compared to the previous one, while the TOC, OSI, NO and PON values were statistically significant ($p<0.05$).Comparing the average scores of the experimental and control groups after the massage; The difference between TOC, OSI, NO averages is statistically significant and lower in the experimental group, while the PON value is significantly higher in the experimental group ($p<0.05$). There was no significant difference in TAC, TOC, OSI, NO and PON between the test and control groups before the massage ($p>0.05$) (Table 2).In the comparison of experimental and control groups; In the experimental group, after the massage, TAC and TOC values significantly decreased, NO and PON values significantly increased ($p>0.05$). There was no significant difference in OSI value between before and after massage in Deney group ($p>0.05$). It is in the control group; The TAS value of the measurement decreased significantly compared to the previous one, while the TOC, OSI, NO and PON values were statistically significant ($p<0.05$).

Conclusion

Restless Leg Syndrome is more common in patients receiving hemodialysis treatment compared to the normal population, with a prevalence of 6-60% [26]. Saraji et al. found in their study that RLS is more common in patients who have been receiving hemodialysis treatment for a long time. It is thought that this situation may be related to the damage caused by neuropathy that occurs in the later stages of patients with end-stage renal failure. In a study conducted in our country, the presence of RLS was detected in 30.8% of patients receiving hemodialysis treatment. In study by Al-Jahdali et al., it was determined that the prevalence of RLS was 50% in patients with renal failure. In their study with 112 hemodialysis patients, RLS was detected in 66.1% of the patients. In the study conducted by Saraji et al. [27]. the prevalence of RLS was reported as 26.6% in patients receiving hemodialysis treatment. In addition, it has been reported that the disease-related complaints are mild or moderate in more than 80% of the patients, and severe or very severe in 16.2%. Although it is a common condition, the causes of this syndrome have not yet been determined [28]. That is, RLS remains a significant problem in patients with CKD and may be related to underlying inflammation. It may be useful to target this pathway. The prevalence of RLS diagnosed using validated measurements is higher than previous reports.Normally, our body keeps these radicals

under control, but sometimes the balance is disrupted and a large number of radicals are formed. In such a situation, free radicals attack, oxidize and damage healthy cells [29, 30]. It is also stated that the oxidative stress-increasing effect of massage hemodialysis applied to these patients gradually increases [31]. Studies have shown that oxidative stress increases and antioxidant capacity decreases in parallel with the increase in hemodialysis duration [32-33].Oxidative stress, autonomic dysfunction and vascular pathologies, which are thought to be related to restless legs syndrome, are frequently seen in RLS patients; Studies have reported that there is a constant oxidative stress in hemodialysis patients [34, 35]. Increased oxidative stress in these patients may cause endothelial dysfunction with atheromatous plaque formation by causing lipoprotein modification and leukocyte stimulation [36]. Therefore, in the study in which we aimed to determine the disease-related lipid peroxidation rates before the massage and the therapeutic massage for RLS, which significantly negatively affects the quality of life, in the comparison of the experimental and control group score averages in the post-massage measurement; While the difference between the averages of RLS, TOC, OSI and NO was statistically significant and lower in the experimental group, the PON value was found to be significantly higher in the experimental group. In the comparison between the experimental and control groups before the massage, no significant difference was found in terms of RLS, TAC, TOC, OSI, and NO. In the intra-group comparison of experiment and control; In the experimental group, after the massage, RLS, TAC and TOC values decreased significantly compared to before the massage, while NO and PON values increased significantly. In other words, RLS is applied to individuals receiving hemodialysis treatment; While massage applied for 10 minutes three times a week for a month was not effective on the oxidative and antioxidant enzymes of the patients, it was observed that the massage applied to both calf muscles for 10 minutes three times a week for a month in the second hour of hemodialysis was effective on the oxidative and antioxidant enzymes of the patients. Because the aggressive molecules formed during the use and metabolism of the oxygen taken into our body are free radicals.

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
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