Changes in the Levels of Serum Beta Endorphin, Serotonin, Adrenaline, Noradrenaline and Dopamine During Smoking Cessation by Electroacupuncture and Nicotine Patch

Elektroakupunktur ve Nikotin Bandı ile Sigara Bırakmada Serum Beta Endorfin, Serotonin, Adrenalin, Noradrenalin ve Dopamin Düzeylerindeki Değişiklikler

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ABSTRACT Objective: The purpose of this study is to investigate the changes in the levels of serum beta endorphin, serotonin, adrenaline, noradrenaline and dopamine during smoking cessation with acupuncture and nicotine patch. **Material and Methods:** This study consists of 42 volunteer persons who applied to quit smoking to Outpatient Family Medicine Clinic of Meram Medical Faculty. The participants were divided randomly into two groups as: 1- Electroacupuncture (EA) group (n=21) and 2- Nicotine patch group (n=21). EA was performed once a day for a period of 30 minutes in the first three days and then once every other day for 30 days. Nicotine patch was applied on the clean, hairless parts of the skin in several steps; for example, 21, 14, and 7 mg for a period of two months. The serum beta endorphin, serotonin, adrenaline, nor adrenaline, dopamine levels were measured before and after acupuncture and nicotine patch therapy. **Results:** When we compare serum serotonin, adrenaline, noradrenaline, dopamine and beta-endorphin levels on the 1st and 30th days in the EA group, we determined that beta endorphin (p=0.000), serotonin (p=0.009), adrenaline (p=0.007) and noradrenaline (p=0.007) levels increased but dopamine (p=0.898) levels did not change. In the nicotine patch group, serum serotonin (p=0.045) levels increased but adrenaline (p=0.318), beta endorphin (p=0.463), noradrenaline (p=0.099) and dopamine (p=0.655) levels did not change. When we compared two groups at the end of 30th day, we found that the serum noradrenaline (p<0.000), dopamin (p<0.028) levels were statistically higher in EA group than nicotine patch group. **Conclusion:** We think that EA and nicotin patch application makes it easy to quit smoking for those trying to give up smoking with psychological support. There was no statistically difference in the rates of smoking cessation in both groups. Therefore, both electroacupuncture and nicotin patch application are effective to stop smoking.

Key Words: Norepinephrine; epinephrine; serotonin; beta-endorphin; smoking cessation

ÖZET Amaç: Bu çalışmada amacımız akupunktur ve nikotin bandı ile sigara bırakma sırasında serum beta endorfin, serotonin, adrenalin, noradrenalin ve dopamin düzeylerindeki değişiklikleri araştırmaktır. **Gereç ve Yöntemler:** Bu çalışma Meram Tıp Fakültesi Aile Hekimliği Polikliniğine sigara bırakmak için müracaat eden 42 gönüllü kişide yapıldı. Katılanlar randomize olarak 2 gruba ayrıldılar. 1- Elektroakupunktur (EA) grup (n=21) ve 2- Nikotin bant grubu (n=21). EA seansları 30 dakika süre ile ilk üç günde günde bir defa ve daha sonra gün aşırı olarak 30 gün uygulandı. Nikotin bandı iki aylık süre içinde derinin temiz ve saçsız kısımlarına, birkaç adımda aşamalı olarak örneğin, 21, 14 ve 7 mg olarak uygulandı. Serum beta endorfin, serotonin, adrenalin, noradrenalin, dopamin düzeyleri EA ve nikotin bandı tedavisi öncesi ve sonrası olarak ölçüldü. **Bulgular:** Serum beta endorfin, serotonin, adrenalin, noradrenalin, dopamin düzeyleri birinci ve otuzuncu günlerde karşılaştırıldığında; EA grubunda, serum beta endorfin (p=0,000), serotonin (p=0,009), adrenalin (p=0,007), noradrenalin (p=0,007) düzeylerinde yükselme belirlenirken, dopamin (p=0,898) düzeyinde değişme olmadı. Nikotin bandı grubunda ise, serum serotonin (p=0,045) düzeyinde yükselme olurken, adrenalin (p=0,318), beta endorfin (p=0,463) noradrenalin (p=0,099) ve dopamin (p=0,655) düzeylerinde değişiklik olmadı. Otuzuncu günün sonunda EA ve nikotin bandı grupları karşılaştırıldığında; EA grubunda serum noradrenaline (p<0,000), dopamin (p<0,028) düzeyleri nikotin bandı kullananlara göre istatistiksel olarak anlamlı derecede yüksek idi. **Sonuç:** EA ve nikotin bandı uygulamalarının sigara bırakmada psikolojik destek sağlayarak sigara bırakmayı kolaylaştıracağını düşünüyoruz. Her iki grupta sigara bırakma oranlarında istatistiksel olarak bir fark yoktu. Bundan dolayı, hem elektroakupunktur, hem de nikotin bandı uygulaması sigara bırakmada etkilidir.

Anahtar Kelimeler: Norepinefrin; epinefrin; serotonin; beta-endorfin; sigarayı bırakma

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Cigarette addiction is the cause of many medical, social, economic and legal problems because of its increasing prevalence in the world and in our country.[1,2] Although cigarette is the most preventable cause of death in the world, one person die of diseases caused by cigarette in every 8 seconds.[3,4] Although the efforts carried out by organizations against smoking in the developed countries and special cessation campaigns have been informing and making the public conscious about the harmful effects of cigarette, and consuming has decreased as a result of legal arrangements, consuming has been increasing in the developing countries including ours. Cigarette manufacturing firms have been going on their intensive commercials and affecting people in many ways. They have especially targeted the developing countries, the youth and women, and they seem to have achieved their aim. The fact that in many researches the starting age of smoking cigarette is often below 20 confirms this.[1-6]

Acupuncture is the oldest and best-known treatment way of traditional Chinese medicine. Acupuncture is especially used in relieving pains, rehabilitating hemiplegia, losing weight, treating mental and psychological illnesses and treating addiction.[7-10] The studies on using acupuncture in addiction cure are relatively new.[11] Various methods such as nicotine band, medicine, nicotine gum, behavior therapy, hypnosis and acupuncture have been used in cigarette cessation treatments.[4,6] Recently, ear and body acupuncture have been used more often. The most significant functional effect of acupuncture is described as the effects of neurotransmitters especially such as beta endorphin, encephalin, adrenaline, nor adrenaline, serotonin and dopamine primarily on the nerve system and other systems.[7-12]

In this study we aimed to find out the effects of the use of electroacupuncture and nicotine patch on giving up smoking.

MATERIAL AND METHODS

STUDY DESIGN, SETTING AND POPULATION

This study consists of 42 volunteers admitted to Outpatient Family Medicine Clinic of Meram Medical Faculty to quit smoking. The participants were randomly divided in two groups as: 1- Electroacupuncture (EA) group (n=21) and 2- Nicotine patch group (n=21).

Before beginning this research, ethical consideration was approved by the ethical committee of Meram Medical Faculty. The participants were informed about the study and written and oral consent were obtained from the volunteers. All participants answered the questionnaire in a face-to-face interview. This questionnaire included sociodemografic characteristics, age, gender, marital status, education, and the status of cigarette smoking (Table 1). The requirements for entry into study were that the subjects should have at least 5 years of regular smoking and on average tobacco consumption should be at least 10 and more ciga-

TABLE 1: Socio-demographic characteristics of participants (n=42).

	Acupuncture (n=21)		Nicotine patch (n=21)	
	n	%	n	%
Gender				
Male	18	85.7	13	61.9
Female	3	14.3	8	38.1
Education status				
Illiterate	1	4.8	1	4.8
Primary school	5	23.8	12	57.1
Middle-high School	5	23.8	3	14.3
University	10	47.6	5	23.8
Participants' employment				
Civil servant	13	61.9	10	47.6
Blue-collar worker	3	14.3	3	14.3
Housewife	3	14.3	5	23.8
Student	2	9.5	3	14.3
Marital Status				
Married	18	85.7	16	76.2
Single	3	14.3	5	23.8
Using alcohol				
No	17	81.0	19	90.5
Yes	4	19.0	2	9.5
Nicotine addiction according to Fagerstrom				
0-2 (very low degree)	1	4.8	1	4.8
3-4 (low degree)	7	33.3	6	28.6
5 (medium)	4	19.1	5	23.8
6-7 (high)	7	33.3	8	38.0
8-10 (very high)	2	9.5	1	4.8

rettes per day. Their height and weight were obtained and body mass indexes were determined.

SMOKING STATUS AND NICOTINE DEPENDENCE

Their current smoking status, the number of consumed cigarettes daily, the initial age of smoking, duration of smoking years, addiction level according to Fagerstorm criteria, smoking prevalence among the children, at home and in the car were determined.[13]

The quick and easy test called the Fagerstrom Test for Nicotine Dependence (developed by Karl Fagerstrom) was used to determine the level of nicotine dependence. In this test, 6 different questions related smoking status were answered. For each question, the points indicated by your answer were written down so that you could determine the total at the end of the test. The results were evaluated **as evidence of** very low, low, medium, high and very high nicotine dependence.[13]

ELECTROACUPUNCTURE TREATMENT

The electroacupuncture (EA) treatment, performed by experienced acupuncturist, was a combination of body, ear electroacupuncture and permanent needle on ear. At first electroacupuncture was performed 30 min once a day for 3 days, later on alternate days, for 30 days. After EA application, permanent ear needles were placed on the Heart and Shen Men points. The body acupuncture needles were 5 cm long and the ear acupuncture needles were 3.5 cm long, with a 0.22 mm diameter. Electrical stimulation was given for 0.05 ms at a 2 Hz frequency at 3 V in a square wave form which had positive and negative alternanses. Electroacupuncture application was performed with a "Biotron" instrument.The electrodes were connected to Lu 7 and LI 4 with St 36 and St 44 on the body symmetrically in pairs.

SELECTED EAR AND BODY ACUPUNCTURE POINTS

The Lung, Heart, Shen Men and Frontal lobe were selected as ear points whereas the Lieque (Lu 7), Hegu (LI 4), Zusanli (St 36), Neiting (St 44) and Taichong (Liv 3) were used as body points. The Heart ear point is the central depression of cavum conchae; the Lung ear point is around the Heart point of cavum conchae; Shen Men point is located at the one third point of the lateral side of the upper edge of the triangular fossa and Forehead is anterior inferior corner of lateral aspect of antitragus. The Lu 7 point is superior to the styloid process of the radius, 1.5 cun above the transverse crease of the wrist. The LI 4 point is found on the dorsal face of the hand between the first and second metacarpal bones and in the middle of the radial side of the second metacarpal bone. The St 36 point is three cun below the patella's bottom edge and between the tibialis anterior muscle and flexor digitorium communis muscle. The St 44 point is between the second and third phalanges on the foot, and the lateral and distal side of the second metatarsodigital joint.

NICOTINE PATCH

Nicotine replacement therapy (NRT) is the remedial administration of nicotine to the body rather than tobacco, usually as part of smoking cessation. The primary benefit of nicotine replacement therapy is that it prevents cravings in a smoker whilst allowing them to abstain from tobacco and thus avoid the harmful effects of smoking. Nicotine patches come in several steps so that users can phase out nicotine use; for example, 21, 14, and 7 mg. A patch is usually worn for 16 or 24 hours, depending on the brand. A new patch is applied to a clean, dry, hairless area of skin on the upper chest, upper arm, or hip as directed by the package directions daily. Avoid areas of irritated, oily, scarred, or broken skin.

EDUCATION

Both groups were informed about the damages of cigarette and ways of quitting smoking and they were given behavioral therapy and trained systematically about their gains in their health when they gave up smoking.

BIOCHEMICAL STUDIES

Before the acupuncture application and nicotine patch and after, 6 ml intravenous blood samples were obtained from the subjects always at the same time in the morning between 9.00 and 10.00 am.

Blood samples were centrifuged at 1000 rpm for 10 minutes in the clinic. The supernatants were obtained and stored at -80° C for further analyses. The serum beta endorphin (BE), serotonin, adrenaline, noradrenaline, dopamine levels were determined using the specific Elisa immunoassay kits (EIA, Phoenix Pharmaceuticals Inc.). Following the measurements with the kits, the levels were determined as "pg/mL" in plasma.

ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee of Meram Medical Faculty of Selcuk University, and an informed written consent was taken from parents of all included subjects.

STATISTICAL ANALYSIS

The SPSS 13.0 statistical software package was used in data entry and analysis. The statistical analysis and evaluations were conducted by the authors. The variables were described by mean, frequency and standard deviation (SD). To compare the statistical significance between groups, Chi-square and independent sample t-test were used. A p value <0.05 was considered as significant.

RESULTS

Of the 42 cigarette smoking cases, 78.3 % (n=31) were male, 26.2% (n=11) female, and 81.0% (n=34) married, and their ages ranged between 18-63 (mean=42.05±11.44). While the rate of smoking cessation with EA was 33.33%, it was 28.57% with nicotine band. There was no statistically difference between the two groups.

SERUM BE, SEROTONIN, ADRENALINE, NORADRENALINE, DOPAMINE LEVELS ON 1st AND 30th DAYS IN EA GROUP

The mean BE levels of the EA group in the pre-treatment and the post-treatment were 0.16±0.04 pg/ml and 0.24±0.08 pg/mL (p=0.000), respectively. The mean serotonin levels in the pre-treatment and the post-treatment were 127.32±25.72 pg/mL and 171.33±71.63 pg/mL (p=0.009), respectively. The mean adrenaline levels of the EA group in the pre-treatment and the post-treatment were 138.70±52.77 pg/mL and 177.82±73.55 pg/mL (p=0.007), respectively. The mean noradrenaline levels of the EA group in the pre-treatment and the post-treatment were 408.08±245.62 pg/mL and 485.95±223.45 pg/mL (p=0.007), respectively. The mean dopamine levels of the EA group in the pre-treatment and the post-treatment were 174.37±35.25 pg/mL and 176.20±49.10 pg/mL (p=0.898), respectively. In the EA group, we determined that beta endorphin, serotonin, adrenaline and nor adrenaline levels increased but dopamine levels did not change (Table 2).

SERUM BE, SEROTONIN, ADRENALINE, NORADRENALINE, DOPAMINE LEVELS ON THE 1st AND 30th DAYS IN THE NICOTINE PATCH GROUP (NPG)

In the nicotine patch group, the mean BE levels in the pre-treatment and the post-treatment were 0.18±0.07 pg/mL and 0.20±0.09 pg/mL (p=0.463), respectively. The mean serotonin levels in the pre-treatment and the post-treatment were 160.02±101.44 pg/mL and 229.20±124.64 pg/mL (p=0.045), respectively. The mean adrenaline levels in the pre-treatment and the post-treatment were 158.83±96.85 pg/mL and 138.31±76.42 pg/mL (p=0.318) respectively. The mean noradrenaline

TABLE 2: Comparison of serum serotonin, adrenaline, noradrenaline, dopamine and beta-endorphin levels on the 1st and 30th days.

	Acupuncture group		Nicotine patch group	
	mean±SD	p	mean±SD	p
Serotonin				
1st day	127.32±25.72	0.009	160.02±101.44	0.045
30th day	171.33±71.63		229.20±124.64	
Adrenaline				
1st day	138.70±52.77	0.007	158.83±96.85	0.318
30th day	177.82±73.55		138.31±76.42	
Noradrenaline				
1st day	408.08±245.62	0.031	104.72±61.54	0.099
30th day	485.95±223.45		130.32±54.64	
Dopamine				
1st day	174.37±35.25	0.898	266.39±182.30	0.655
30th day	176.20±49.10		290.25±209.89	
Beta-endorphin				
1st day	0.16±0.04	0.000	0.18±0.07	0.463
30th day	0.24±0.08		0.20±0.09	

levels of the NPG group in the pre-treatment and the post-treatment were 104.72±61.54 pg/mL and 130.32±54.64 pg/mL (p=0.099), respectively. The mean dopamine levels in the pre-treatment and the post-treatment were 266.39±182.30 pg/mL and 290.25±209.89 pg/mL (p=0.655), respectively. In the nicotine patch group, merely serotonin levels increased significantly but adrenaline, nor adrenaline and dopamine levels did not change (Table 2).

The comparison of serum BE, serotonin, adrenaline, noradrenaline and dopamine levels on the 30th day in acupuncture and nicotine patch groups were shown in Table 3. The serum noradrenaline (p<0.000), dopamin (p<0.028) levels were higher among EA group than the nicotine patch group. There was no difference in serum beta-endorphin, serotonin, adrenaline levels in EA when compared with the nicotine patch group (Table 3).

DISCUSSION

Before discussing the results, the limitations of the present study must be considered. Our study indicates a small group. Therefore, to prevent and reduce smoking, further researches and more effective smoking cessation programs should be carried out among larger groups.

In this study, we determined that beta endorphin, serotonin, adrenaline and nor adrenaline levels increased but dopamine levels did not change in the EA group. In the nicotine patch group, merely serotonin levels increased significantly but adrenaline, nor adrenaline and dopamine levels did not change. While the rate of quitting smoking with EA was 33.33% (n=7), it was 28.57% (n=6) with nicotine band. There was no statistically difference between the two groups for quitting smoking (p>0.05). Tobacco contains nearly 4000 ingredients including nicotine, aromatic hydrocarbons N-nitrosamine, aromatic amines, formaldehyde, benzene and inorganic compounds. Nicotine stimulates the release of mediators such as noradrenaline, acetylcholine, dopamine, 5-hydroxytryptamine, γ-aminobutyric acid and endorphins. The dopaminergic system ("reward system") in particular is influenced by nicotine.[14]

Ear and body acupuncture have been used at the clinics where addiction therapy is carried out. In particular, the ear point "lung" and "Heart" have proved to be very effective in the treatment of withdrawal symptoms and should be included in any program of relapse prevention. These points have a unique location at the most superficial branch of the vagus nerve. Stimulation of the vagus nerve by using these points are believed to produce neural impulses that restore activity of the nervous cells of the reticular formation that, in turn, stimulate the hypothalamus, which initiates the reward cascade. Investigator have hypothesized that acupuncture relieves withdrawal symptoms by triggering the body to produce more endorphins, thus bringing the body back to equilibrium.[15,16] The stimulation of acupuncture point St 36 revealed significant increases in 5HT synthesis and utilization. The stimulation of the Shen Men point regulates cerebral cortex function and it has a sedative effect.[17] The stimulus of Liv 3, a body acupuncture point, causes sedation.[18] In our study, Lung and Shen Men were used as ear points and St 36 ve Liv 3 points were used as body points.

Pan et al. have studied the changes in the levels of ACTH and beta endorphin in the hypophysis anterior lobe and plasma caused by EA in a study carried out on rats. The levels of ACTH and beta endorphin increased in the hypophysis anterior

TABLE 3: Comparison of serum serotonin, adrenaline, noradrenaline, dopamine and beta-endorphin levels on the 30th day in acupuncture and nicotine patch groups.

	Acupuncture group mean±SD	Nicotine Patch group mean±SD	p*
Serotonin			
30th day	171.33±71.63	229.20±124.64	0.082
Adrenaline			
30th day	177.82±73.55	138.31±76.42	0.104
Noradrenaline			
30th day	485.95±223.45	130.32±54.64	0.000
Dopamine			
30th day	176.20±49.10	290.25±209.89	0.028
Beta-endorphin			
30th day	0.24±0.08	0.20±0.09	0.192

*According to Independent Samples t-test.

lobe and plasma was detected.[19] It has been stated that beta endorphin, the endogen opioids whose level increase in the central nerve system and plasma with acupuncture application, help to improve mental and psychological state and remove anxiety.[17] In our study, we similarly observed an increase in serum beta endorphin level following EA application at 2 Hz frequency in the EA grup.

Clavel-Chapelon and his colleagues examined the success rate at smoking cessation following the treatment with acupuncture and nicotine gum for four years on 996 subjects smoking ten or more cigarettes a day.[20] They applied acupuncture from Bitong and Shuaigou (Du 26) points on the 1st, 7th, 28th days. The treatment of nicotine gum was applied by 2 mg gums and 30 gums a day at the most were used in the first six months. They observed that the success rate at smoking cessation in a group of 540 persons in which the treatment of acupuncture was applied for a month, a year and four years was successively 22%, 8.8%, 5.6%. The success rate at smoking cessation in a group of 481 persons in which the treatment of nicotine gum was applied for a month, a year and four years was 26.2%, 11.1% and 6.1% successively.[20]

He and his colleagues investigated the efficacy of acupuncture treatment in smoking cessation.[21] In this study, they applied acupuncture treatment pertaining to smoking cessation on 26 voluntary subjects smoking 20±6 cigarettes a day (test group) and acupuncture treatment not pertaining to smoking cessation on 20 voluntary subjects (control group). He and his colleagues performed 2 seances a week to test and control groups for 3 weeks. They applied electroacupuncture to Lieque (Lu 7) and Kongzui (Lu 6) body points; acupuncture to Shen Men, Mounth, Lung ear points; acupress to Shen Men, Mounth, Lung, Trachea, Hunger and Endocrine ear points. In control group, they also applied electroacupuncture to body points; and acupuncture and acupress to ear points not pertaining to smoking cessation. Acupress application was made 4 times a day in both groups when smoking tendency occured. While 31% of the test group gave up smoking as a result of these applications, nobody in the control group could give up smoking. He and his colleagues determined that the application made to acupuncture points pertaining to smoking cessation was more effective than the application made to points not pertaining to smoking cessation.

The fact that the ratio of giving up smoking was 33.33% in our study being much higher than the ratio of Clavel-Chapelon et al. can be attributed to EA with regular training program, to different points used, duration of therapy and to the frequency of sessions.

Bier et al. researched the subjects in three groups and used the right acupuncture at the points to quit smoking in the first group (Test Group 1), right acupuncture and cigarette cessation uraining in the second group (Test Group 2) and they applied the acupuncture at the points which were not helpful to give up smoking and cigarette cessation training in the third group (Test Group 3).[22] Test group 1 received right acupuncture from the Shen Men, Sympathetic, Lung, Kidney and Liver points on the ear 5 sessions a week for 4 weeks. Test group 2 received cigarette cessation training in addition to the acupuncture points of test group1. It was observed in cigarette cessation therapy that using right acupuncture accompanied by training as in the test group 2 was relatively more effective on quitting smoking than using only right acupuncture as in the test group1 and 3.[22] As in the study of Bier et al, if we include systemic training program in EA and nicotine patch groups, the therapies of giving up smoking can be more effective when compared with other studies.

Nicotine causes serotonin, noradrenaline and adrenaline levels to increase in the brain tissue and plasma. Smoking cessation also causes disorders in the body because of nicotine deprivation; that is, low level of serotonin, noradrenaline and adrenaline.

Cummings et al. emphasized that the 7-day nonsmoking prevalence rate measured at 12 months among callers who received the nicotine patches was 1.78 times higher than the individuals who did not receive nicotine patches.[23]

Alberg et al. declared that 30% of NRT ever users compared to 39% of nonusers had quit smok-

ing ($p<0.01$). Among persistent smokers, the likelihood of reducing the number of cigarettes smoked per day was similar between NRT ever users (40%) and nonusers (41%).[24]

As in this study, we think that beta endorphin, serotonin, adrenaline and noradrenaline levels increase with EA application, makes it easy to quit smoking for those trying to give up smoking by psychological support, behavioral treatment, education. In the same time, we think that serotonin level increase with nicotin patch application, makes it easy to quit smoking for those trying to give up smoking by psychological support. While the rate of smoking cessation with EA was 33.33%, it was 28.57% with nicotine band. There was no statistically difference between the two groups. Therefore, both EA and nicotin patch application are effective in approximately the same rate.

As a result, EA application seems to have the same effect as nicotine band use. We determined no statistical differences in quitting smoking between both groups ($X2=0.791$, $p=0.374$).

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