Electroacupuncture Therapy in Nicotine Dependence: A Double Blind, Sham-Controlled Study

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ABSTRACT

Introduction: The number of non-pharmacological controlled studies is insufficient in the treatment of nicotine dependence (ND). Nevertheless, non-pharmacological treatments, such as electroacupuncture (EA), are becoming increasingly popular in the treatment of ND. The aims of this study were to determine the efficacy and safety of "true EA therapy" (TEAT) compared to those of "sham EA therapy" (SEAT) in ND treatment.

Methods: Eligible patients who met the DSM-IV criteria for ND (n=450) were included in the study. This study was a double-blinded, sham-controlled clinical trial with a 4-week treatment period and 4-week follow-up conducted between June and December 2009 at a psychiatry outpatient clinic. One hundred and sixty four adult (≥ 18 years; 44 men, 120 women) cigarette smokers out of 450 patients who met the inclusion and exclusion criteria were enrolled in the study in a ratio of 1:1 to receive TEAT (n=84) or SEAT (n=80). Routine biochemical and hematological tests, chest X-Ray, and ECG were carried out; end-expired carbon monoxide (CO) levels were measured too. Clinical characteristics were obtained through the Fagerström Nicotine Dependence Test (FNDT), Hamilton Rating Scale for Depression (HRSD), and Hamilton Anxiety Scale (HAS). EA was carried out by a trademark device, Antismoke

3000®. Efficacy analyses were performed on "intent-to-treat analysis." Primary outcome was the differences from baseline to endpoint in mean FNDT, number of cigarettes smoked per day, and CO levels at week 4. Secondary outcomes were the same variables at week 8. These variables were assessed via analysis of covariance (ANCOVA).

Results: Mean baseline FNDT, HRSD, HAS, and CO levels of the groups were statistically similar. TEAT and SEAT groups demonstrated no significant changes in the outcome variables and smoking cessation rates (35.7% and 30%, respectively). Of those remaining outside of the study, 8.3% were from the TEAT group and 8.7% were from the SEAT group; there was no statistical difference between the groups. The rate of treatment discontinuation was similar between the TEAT (44%) and SEAT (43.7%) groups ($p>0.05$). The rates of adverse events were not similar too.

Conclusion: This study showed that both TEAT and SEAT have similar efficacy and safety profiles in patients with ND.

Keywords: Nicotine dependence, cigarette, acupuncture, electroacupuncture

INTRODUCTION

Nicotine dependence (ND) is a global health problem with devastating outcomes (1). In the treatment of ND, in addition to pharmaceutical therapies, a range of therapeutic choices including acupuncture, psychotherapy, and education have been attempted. While a large number of double-blind controlled studies have been conducted with drug therapy, the number of controlled studies regarding non-pharmacological therapies is insufficient (2). It is noticeable that despite the lack of sufficient evidence, a number of methods such as homeopathy, hypnosis, neuro-electric therapy (NET), transcranial electrotherapy, and electroacupuncture (EA) are commonly used in the treatment of ND (3). In one study, data about the improvement of withdrawal symptoms after applying NET for 10 days have been reported (4). In some articles, it is claimed that classical acupuncture together with education applied in ND treatment can achieve positive results (5).

Over the last years, it has been observed that somewhat modified traditional acupuncture in the appearance of EA has been used more often in ND therapy. As is known, in electroacupuncture, specific points of the body are electrically stimulated by using a probe (6).

In some studies, even if they report the efficacy of traditional acupuncture and EA in ND therapy, the results are contradictory (7,8,9,10). Sources of these contradictions may be found in methodological differences regarding the criteria for patient recruitment, the specific application of acupuncture and EA, the acupuncture points used, and the duration of treatment. The sampling and standardization issues observed in such studies have raised the question if "true EA treatment" (TEAT) or "sham EA treatment" (SEAT) is more effective and safer.

Despite the contradictory and insufficient findings, the use of EA in ND therapy is fast increasing. Until this day, no systematic double-blind placebo-controlled study concerning the efficacy and safety of EA in ND therapy using a method like the one presented in detail below has been conducted. The present study was conducted to bridge this gap. Our hypothesis was that the efficacy and safety of TEAT and SEAT do not differ from each other.

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METHODS

Sampling

The study was initiated after obtaining approval from the Ethics Committee of Göztepe Training and Research Hospital in Istanbul and the Ethics Advisory Committee of Erenköy Training and Research Hospital for Mental and Nervous Disorders. The study population consisted of all patients who applied to the Cigarette Dependence Polyclinic between June and December 2009 (n=534). These patients received detailed information about the study and all of them were asked to provide a written consent. Thirty-nine patients did not provide their consent and were thus excluded. Of the remaining 495 patients, 45 were excluded because they did not match the diagnosis criteria of ND according to the DSM-IV of the American Psychiatric Association (11). The remaining with a diagnosis of ND (n=450) constituted the study sample. After receiving written consent, these 450 patients were included. Conditions for the inclusion of patients with a diagnosis of ND in the study were as follows: aged between 18 and 65 years, having at least once gone through an unsuccessful attempt to quit smoking, and having smoked at least 10 cigarettes per day for the last year. Of these 450 patients, 142 were excluded; 60 were excluded for reasons such as bipolar disorder (n=23), psychotic disorder (n=20), major depression (n=12), and other mental disorders (n=5), and 82 were excluded because of any other medical condition. Also, patients receiving regular treatment with psychotropic or other medications (n=75) were excluded. Patients whose laboratory test results showed pathological values (n=48) were excluded, as were those whose medical history included significant diseases such as epileptic episodes, heart disease, or cardiovascular diseases (n=21). Altogether, of the 450 patients, 286 were excluded for the reasons mentioned above. The remaining 164 (44 male, 120 female) were included and were evenly divided by one of the researchers (Dr. S. K.) into two groups by drawing lots. For four weeks, the patients received double-blind TEAT (n=84) or SEAT (n=80). Sampling and work flow details are presented in Figure 1.

Procedures

Visit 0 (baseline visit): During this visit, a detailed medical history of the 164 patients was recorded as were sociodemographic features and the number of cigarettes smoked daily; also, the end-expired carbon monoxide (CO) levels were measured. For all patients, basic biochemical examinations (including hemogram, full urine test, blood sugar, blood urea nitrogen, electrolyte, total cholesterol, total triglyceride, LDL, HDL, liver enzyme, and thyroid hormone levels), chest X-ray, ECG, and psychiatric tests as specified below were performed, and they were directed to EA therapy.

Visit 1 was done 1 day after Visit 0, Visit 2 after 3 days, Visit 3 after 7 days, and Visit 4 after 30 days. Including the baseline visit, altogether, 5 visits took place. In Visit 1, 2, 3, and 4, before undergoing TEAT or PEAT, the patients took 3 psychiatric tests (specified below), their end-expired CO levels were measured, and the number of cigarettes smoked per day was recorded. In order to determine early relapse, patients were reassessed 1 month after Round 4, and the basic examinations and tests conducted at Visit 0 were repeated. These procedures were performed by a researcher (Dr. S. G.) who was blinded regarding the group membership.

Electroacupuncture Applications

After completing the assessments specified above, patients directed toward EA were evenly distributed between the TEAT (n=84) and SEAT groups, respectively. We attempted to achieve similarity in the numbers of patients to be assigned to each group. The patients were not told which group they belonged to.

TEAT and SEAT procedures were applied in a seemingly similar manner. In both TEAT and SEAT, a trademark instrument, Antismoke 3000®, was used. During the application, the patients were made to sit relaxed in a half-extended position. The application points were established using the recommendations of the instrument's manufacturer. Accordingly, 19 points on the right auricle, 18 on the left auricle, and 3 at the tip of the nose were stimulated in turn. In the TEAT procedure, the settings recommended for an effective signal of 10 Hz, 0.50–0.80 mA, and 1 K Ω direct

Figure 1. Patient flow diagram. *: Patients who gave written consent, matching the DSM-IV criteria, completing the first assessment (Visit 0). ^b: Patients being late for the visits (n=5) or starting the use of bupropion (n=8) or varenicline (n=4). ^c: Patients being late for the visits (n=3) or starting the use of bupropion (n=4) or varenicline (n=6). ^d: Quality of data being insufficient (n=5) or no data except for Visit 0 (n=2). ^e: Quality of data being insufficient (n=4) or no data except for Visit 0 (n=3). ^f: Patients attending Visit 0 and at least 1 further visit, ND: nicotine dependence.

current were used. The application through a round-tipped probe at each of the above specified points lasted for approximately 20 s. One EA treatment was completed in 15 min. The SEAT procedure was conducted in a way similar to the TEAT procedure; however, the signal used was set to a frequency of <1 Hz of electric current, which is accepted as being at the placebo level. The therapies were administered by an experienced nurse trained in performing EA procedures.

Psychiatric Scales and Parameters Used

1) Sociodemographic Data Form: A 20-item form prepared to record the patients' smoking behavior and related medical and mental conditions.

2) Fagerström Nicotine Dependence Test (FNDDT): This 6-point scale measures the severity of tobacco dependence (12). It has often been chosen in therapy efficacy studies and was therefore used here. A study of the validity and reliability of the scale in Turkey has been realized (13). In this test, "number of cigarettes smoked per day" was used as a separate parameter.

3) Hamilton Rating Scale for Depression (HRSD): This scale, developed by Hamilton, is used in a 17-item form. It is used to measure the level of depression frequently observed in ND patients. A study of the validity and reliability of the scale in Turkey has been conducted by Akdemir et al. (14).

4) Hamilton Anxiety Rating Scale (HAM-A): This scale was developed by Hamilton, and it is used to measure the level of anxiety frequently observed in ND patients. A study of the validity and reliability of the scale in Turkey has been conducted by Yazıcı et al. (15).

5) End-expired carbon monoxide (CO) level: This is obtained by measuring CO levels in the air expelled during expiration. This method is used to establish both ND and smoking cessation (16). CO levels are measured by a device mounted on the Antismoke. This device can measure CO levels between 0 and 500 ppm. It is accepted that a value of >6 ppm demonstrates cigarette smoking with a specificity of 96% and a sensitivity of 94% (16). In this study, for the response to treatment (quitting cigarettes), Middleton and Morice (17) rules were taken into consideration. In line with these, smoking <1 cigarette per day and a CO level of <6 ppm was accepted as a positive response to the therapy.

Statistical Analysis

On the assumption that the standard deviation of FNDDT values is <3.2, it has been calculated that for a study with the power of 80% ($\alpha=0.05$), 121 patients are sufficient. However, considering that up to 40% leave the treatment, the sample size has been kept high. Effectiveness analyses were performed using data from patients attending Visit 0 and at least 1 further visit. Data for patients not attending the last visit have been calculated with the "Last Observation Carried Forward" (LOCF) method. In the effectiveness analyses, the number of cigarettes smoked daily in both groups and differences in FNDDT values and CO levels between the baseline and the last visit were used. Effectiveness analyses were performed using analysis of covariance (ANCOVA). If FNDDT and CO levels were reduced by >50%, patients were assessed as having responded to the therapy. The descriptive statistics involved Pearson's correlation test and chi-square and t-tests. All numerical values are presented in the form of mean $\pm$ standard deviation. For statistical significance, $p<0.05$ was considered.

RESULTS

Sociodemographic and Clinical Specifications

Some sociodemographic and clinical specifications of the groups are shown in Table 1. These specifications were similar between the groups.

The average period of therapy participation in the TEAT and SEAT groups was 3.7 and 3.9 weeks, respectively. Of the 164 patients, 93 (56.7%) completed the 4-week therapy program. However, 14 (8.5%) were excluded for various reasons. The ratio of patients excluded from both the groups was similar (for TEAT, $n=7$, 8.3%; for SEAT, $n=7$, 8.7%; $\chi^2=0.74$, $df=2$, $p>0.05$). Detailed numbers are presented in Figure 1. As a result of Pearson's correlation analysis, significant correlations were established between FNDDT and HRSD ($r=0.26$, $p<0.01$), HAS ($r=0.20$, $p<0.01$), CO ($r=0.21$, $p<0.01$), daily cigarette intake ($r=0.63$, $p<0.01$), and packets smoked per year ($r=0.43$, $p<0.01$) values.

Response to Treatment in the Groups

In both the groups, daily cigarette intake and values for FNDDT and CO showed a downward trend over time. However, the reductions were found to be similar between the groups. (ANCOVA, $F=2.08$, $df=1$, 191, $p=0.08$) (Figure 2). Further, no difference between the groups was found regarding the reduction in daily cigarette intake ($F=1.9$, $df=1$, 191, $p=0.12$) and amount of CO value reduction ($F=2.21$, $df=1$, 191, $p=0.07$) (Figure 3). The HRSD ($F=2.18$, $df=1$, 191, $p=0.07$) and HAS values ($F=2.07$, $df=1$, 191, $p=0.08$) did not show any change over time.

The ratio of smoking cessation by Visit 4 between the TEAT ($n=30$, 35.7%) and SEAT ($n=24$, 30%) groups was similar. Smoking cessation ratios by sex were also similar. An assessment was performed 1 month after Visit 4 to establish early relapse and there was no change in cessation rate; it was similar in the TEAT ($n=30$, 35.7%) and SEAT ($n=24$, 30%) groups ($\chi^2=0.60$, $df=1$, $p=0.57$).

Tolerability

The rate of patients withdrawing from the study in the TEAT ($n=37$, 44%) and SEAT ($n=35$, 43.7%) groups was similar ($\chi^2=0.89$, $df=1$, $p=0.91$). Detailed numbers are presented in Figure 1. The rate of side effects reported by the patients was similar (Table 2). In both the groups, the most reported side effect was tremor of the hands. The ratio of patients

Table 1. Some baseline sociodemographic and clinical features of the groups

Variables	TEAT (n=84)	SEAT (n=80)	t / χ^2	p
Age	46.82 $\pm$ 12.94	43.74 $\pm$ 13.25	1.51	0.13
Sex (M/F)	65/19	55/25	1.55	0.21
ASS	19.74 $\pm$ 5.85	17.93 $\pm$ 4.86	1.78	0.06
ADCS	23.02 $\pm$ 11.70	22.93 $\pm$ 10.84	0.05	0.95
Packets smoked per year	30.82 $\pm$ 20.84	31.97 $\pm$ 22.16	0.34	0.74
HRSD	5.23 $\pm$ 3.98	4.90 $\pm$ 3.92	0.40	0.68
HAS	8.57 $\pm$ 5.49	7.25 $\pm$ 4.63	1.67	0.13
FNDDT	5.14 $\pm$ 2.45	5.15 $\pm$ 2.56	0.07	0.94
CO (ppm)	13.60 $\pm$ 1.18	13.52 $\pm$ 1.09	0.39	0.69

M: male; F: female; ASS: age at starting smoking; ADCS: average daily cigarette smoked; HRSD: Hamilton Rating Scale for Depression; HAS: Hamilton Anxiety Scale; FNDDT: Fagerström Nicotine Dependence Test; CO (ppm): end-expired carbon monoxide (parts per million)

Figure 2. Change of FNDT points between the groups (LOCF). No significant difference was found between the groups ($p=0.08$).

FNDT: Fagerström Nicotine Dependence Test

Figure 3. Change of time of average daily cigarette smoked (ADCS) for both the groups (LOCF). No significant difference was found between the groups ($p=0.96$).

withdrawing from the study because of side effects was similar between the TEAT ($n=5$, 5.9%) and SEAT ($n=5$, 6.2%) groups ($X^2=0.93$, $df=1$, $p=0.94$).

DISCUSSION

Pharmacological agents are frequently used in the treatment of ND (18). However, for various reasons, an increase in the use of non-pharmacological therapies has been observed. The lack of sufficient studies on the effectiveness and safety of non-pharmacological methods makes it difficult to reach a clear judgement regarding these approaches.

The present study found the effectiveness of TEAT and SEAT to be similar. The fact that in both the groups, 30% participants gave up smoking can be explained through the patients' motivation (19). One study on this topic found that EA is not effective in ND therapy (6). However, there are some methodological differences between that study and our results. Most importantly, in the cited study, no placebo was used and the points on the auricle where electrical stimulation was applied were anatomically different, as were the duration and frequency of the applied electrical stimuli. Despite the mentioned differences, the resulting similarities suggest that the effectiveness of EA in ND treatment is open to speculation.

However, a different study reported that a 4-week traditional acupuncture treatment combined with a 5-week education program was effective for the reduction of cigarette intake and cessation (5). In this study, acu-

Table 2. Side effects reported by patients in the TEAT and SEAT groups

	TEAT (n, %)	SEAT (n, %)	X ²	df	p
Nervousness	30 (35.7)	32 (40)	1.45	1	0.57
Restlessness	33 (39.3)	33 (41.2)	0.79	1	0.82
Lack of attention	39 (46.4)	39 (48.8)	0.81	1	0.84
Sleeplessness	36 (42.9)	34 (42.5)	0.08	1	0.98
Fatigue	42 (50)	35 (43.8)	1.63	1	0.34
Increased appetite	29 (34.5)	33 (41.2)	1.73	1	0.31
Tremor of hand	46 (54.8)	44 (55)	0.91	1	0.89
Palpitation	46 (54.8)	38 (47.5)	1.78	1	0.29
Constipation	46 (54.8)	38 (47.5)	1.82	1	0.19

TEAT: true electroacupuncture therapy; SEAT: sham electroacupuncture therapy

puncture on the auricle with a traditional method was applied alongside education. The study design however does not allow ascertaining to what extent the improvement was related to the acupuncture or to education. Therefore, the difference between the results from that study and from ours can be attributed to methodological differences. Until now, no standard acupuncture method has been reported to be more effective than others (9). A meta-analysis conducted during the previous years showed that classical acupuncture is effective in ND treatment; yet, the use of different points does not change the effectiveness (20). If the same result also applies to EA will become clearer when more studies similar to ours collect relevant data.

Both with traditional acupuncture and EA, the mechanism of action in ND therapy is unclear. It is debatable how mechanical or electrical stimulation applied to the ear or tip of the nose affect the smoking behavior. It has been suggested that the effectiveness of EA and traditional acupuncture can be explained through changes in certain neurotransmitter and neuromodulator systems due to the stimulation of specific points (21,22,23,24). Some studies report that repetitive high-frequency transcranial magnetic stimulation (rTMS) can reduce cigarette use, ND, and craving for nicotine (25).

It may be interesting to ask if in ND therapy, pharmacological or non-pharmacological methods are more effective. Studies on drugs show that pharmacological substances are more effective than placebos. One survey demonstrated that nicotine patches have an effectiveness of between 18% and 77% in ND treatment; these rates are twice as high as those of placebos (26). However, it is not known if the improvements reached through the use of drugs continue in the long term. Therefore, it has been reported that for a long-term effect, a combination of medication and behavioral therapy is important (19). Our study showed that after 1 month of therapy, approximately 30% patients quit smoking. One month after the last consultation, this rate was shown to be stable. The rate we found was lower than that achieved through medication. In addition, it is unclear how this rate will change in the long term, but it can be assumed to decrease.

In this study, the rate of patients withdrawing from the intervention was similar between the groups. This suggests that there was no difference in tolerability between the two groups. These results can be connected to the generally high non-compliance of ND patients, irrespective of the treatment method. The most frequently reported side effect in this study was tremor of the hands. However, although this symptom was reported by the patients as a side effect, it should not be forgotten that tremor of the hands can be caused by reducing the number of cigarettes smoked or cessation of smoking. Further, it is unclear if the other symptoms listed in

Table 2 are side effects or withdrawal symptoms caused due to smoking cessation. However, given that the rate of side effects reported in the two groups was similar, it may be thought that they can rather be caused by the cessation of smoking.

One of the most important limitations of this study is that the EA application frequency was kept stable during all consultations and that the total duration of the treatment was relatively short. When we look at studies using stimulation frequencies of up to 100 Hz with a total duration of treatment of 3 months (7,8,9,10), it can be said that different methods achieved varied results. However, it can be seen that the effectiveness of both traditional acupuncture and EA in ND treatment will continue to be discussed. The discussion of the mode of action of acupuncture in ND treatment and the debate over standardization issues may not come to an end in the near future.

This study showed that the effectiveness of EA in ND therapy is at the level of placebo. The results suggest that it is adequate for the Ministry of Health to request scientific effectiveness and safety analyses for EA and similar instruments being introduced to the marketplace in Turkey.

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