Original Article / Özgün Araştırma

The clinical efficiency of acupuncture in preventing migraine attacks and its effect on serotonin levels

Akupunturun migren ataklarının önlenmesinde klinik etkinliği ve serotonin düzeylerine etkisi

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ABSTRACT

Objectives: This study aims to investigate the efficacy of acupuncture in preventing migraine attacks.

Patients and methods: Between December 2013 and June 2014, a total of 54 patients with a diagnosis of migraine in our neurology clinic were randomized into two groups. Venlafaxine was administered for three months to one group (drug therapy group: 4 males, 21 females; mean age 32.0±9.1 years; range, 18 to 65 years), while the other group was treated with acupuncture (acupuncture group: 5 males, 24 females; mean age 30.3±7.4 years; range, 18 to 65 years). The control group consisted of a total of 29 healthy individuals (7 males, 22 females; mean age 30.3±7.4 years; range 18 to 65 years). Blood serotonin levels were assessed before and after treatment along with visual analog scale (VAS) and Migraine Disability Assessment (MIDAS) in both groups.

Results: There was no statistically significant difference in the mean analgesic use before and after the treatment and VAS and MIDAS scores between the acupuncture and drug therapy groups (p>0.05). The number and duration of attacks was found to be significantly lower in both groups, compared to the pre-treatment values (p<0.0001). The serotonin levels in the acupuncture and drug therapy groups were significantly higher compared to the pre-treatment values (p<0.001). Serotonin levels were found to be significantly lower in healthy individuals compared to the study groups (p<0.0001).

Conclusion: Based on our study findings, acupuncture may be an effective option in the migraine prophylaxis.

Keywords: Acupuncture; migraine; serotonin.

ÖZ

Amaç: Bu çalışmada akupunturun migren ataklarının önlenmesindeki etkinliği araştırıldı.

Hastalar ve yöntemler: Aralık 2013 - Haziran 2014 tarihleri arasında nöroloji kliniğimizde migren tanısını konan toplam 54 hasta rasgele iki gruba ayrıldı. Bir gruba (ilaç tedavisi grubu: 4 erkek, 21 kadın; ort. yaş 32.0±9.1 yıl; dağılım 18-65 yıl) üç ay süreyle venlafaksin uygulanırken, diğer grup (akupunktur grubu: 5 erkek, 24 kadın; ort. yaş 30.3±7.4 yıl; dağılım 18-65 yıl) akupunktur ile tedavi edildi. Kontrol grubu 29 sağlıklı bireyden (7 erkek, 22 kadın; ort. yaş 30.3±7.4 yıl; dağılım 18-65 yıl) oluşuyordu. Her iki grupta da görsel analog ölçeği (GAÖ) ve Migren Özürlülük Değerlendirmesi (MIDAS) ile birlikte tedavi öncesi ve sonrası kan serotonin düzeyleri ölçüldü.

Bulgular: Akupunktur ve ilaç grubu arasında tedavi öncesi ve sonrası ortalama analjezik ilaç kullanımı ve GAÖ ve MIDAS skorları açısından istatistiksel olarak anlamlı fark saptanmadı (p>0.05). Atak sayı ve süresi, her iki grupta da tedavi öncesi değerlere kıyasla, anlamlı düzeyde düşük bulundu (p<0.0001). Akupunktur ve ilaç grubunda serotonin düzeyleri, tedavi öncesi değerlere kıyasla, anlamlı düzeyde yüksekti (p<0.0001). Çalışma gruplarına kıyasla, sağlıklı bireylerin serotonin düzeyleri, anlamlı düzeyde düşük bulundu (p<0.0001).

Sonuç: Çalışma bulgularımıza göre, akupunktur, migren profilaksisinde etkili bir seçenek olabilir.

Anahtar sözcükler: Akupunktur; migren; serotonin.

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Migraine is a headache disorder characterized by recurrent attacks. Prophylactic treatment constitutes an important aspect of migraine management. Migraine often affects social and work life, leading to excessive use of analgesics. Prophylactic treatment is predominantly used to reduce frequency, duration and severity of attacks. It reduces the utilization of acute treatment improving the patient's functional state. Furthermore, it may prevent transformation of episodic migraine to chronic migraine and reduce health expenditures.[1] Neurovascular, biochemical and thrombolytic theories have been proposed as implicated in the pathogenesis of migraine attacks.[2,3] Acupuncture, widely used in Eastern countries, is recently gaining popularity in Western countries. Acupuncture has a long history of use in the treatment of many pain conditions, including headache.[4] Acupuncture stimulation causes a release of endorphins, serotonin, enkephalins, gamma-aminobutyric acid, norepinephrine and dopamine which help explain the effect of acupuncture on a biomedical and pharmacological basis.[4,5]

The purpose of this study is to measure serotonin levels in blood after acupuncture treatment in migraine patients and investigate the efficacy of acupuncture in the prophylaxis of migraine.
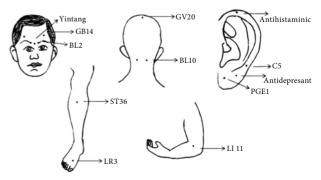
PATIENTS AND METHODS

A total of 250 patients who received a diagnosis of migraines from the Neurology outpatient clinic at our hospital were enrolled in the study. Fifty-four patients who fulfilled the inclusion criteria and completed the follow-up visits were eligible for the study.

A total of 54 migraine patients, who consulted at the Neurology Outpatient Clinic of Bakirkoy Dr. Sadi Konuk Education and Research Hospital between December 2013 and June 2014 and were diagnosed as migraine according to the diagnostic criteria of the International Headache Society (IHS) (2004) were evaluated. Patients fitting the inclusion criteria were enrolled in the study. The inclusion criteria were as follows: both male and female gender, age between 18 and 65 years, migraine diagnosis for more than two years, the presence of migraine attacks before the age of 50 and having four or more attacks within the past three months.

Ethics committee approval was obtained by the Ethics Board of Bakirkoy Dr. Sadi Konuk Education and Research Hospital (Date: 14.07.2014 Resolution No. 2014-09-14). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who accepted to participate, were enrolled in the study after signed informed consent was obtained, and were randomized to drug treatment group (4 males, 21 females; mean age 32.0±9.1 years; range 18 to 65 years) and acupuncture group (5 males, 24 females; mean age 33.76±7.82 years; range 18 to 65 years) using a computer-generated, random block design. Twenty-nine age- and sex-matched healthy subjects (7 males, 22 females; mean age 30.3±7.4 years; range 18 to 65 years) were admitted to study, who received no treatment (Figure 1).

Among these patients, 25 were treated with venlafaxine 75-225 mg/day for a period of three months. Patients suffering from other types of headache (tension type, cluster and secondary headache) or other neurological diseases; for example, patients with chronic disorders such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, coronary artery disease and liver disease were excluded from the study. Also, patients who were pregnant, using insufficient contraception, history of antipsychotic agents or antidepressants use within the last three months, patients suffering from painful periods longer than 15 days a month and history of excessive use of drugs or alcohol abuse or history of head trauma were excluded from the study.
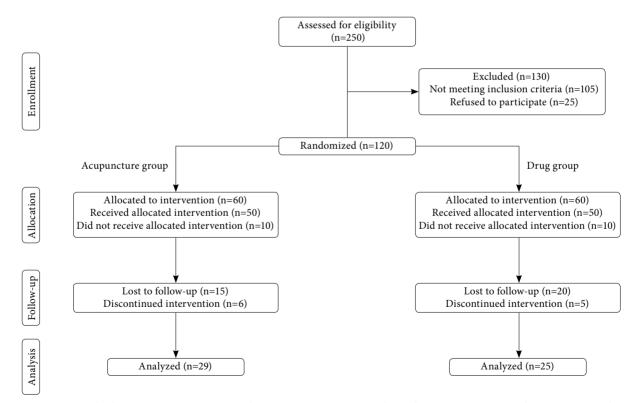
Pre-treatment and post-treatment headache frequency and duration, analgesic drug and triptan usage were evaluated using visual analog scale (VAS) and Migraine Disability Assessment (MIDAS).[6] Demographic and clinical characteristics of the patients were recorded prior to the treatment. The acupuncture treatment was administered in a total of 26 sessions, first three days a week (12 sessions), then two days a week. The

Figure 1. Randomized clinical trial comparing acupuncture with drug therapy for migraine (CONSORT diagram). Participants with migraine were randomized to receive either acupuncture (n=29) or drug therapy (n=25). GB14: Gall Bladder14; BL2: Bladder2; ST36: Stomach36; LR3: Liver 3; GV20: Governing Vessel20; BL10: Bladder 10; PGE1: ProstaglandinE1; LI 11: Large Intestine 11.

acupoints were selected in accordance with the related literature and textbooks.[7,8] All acupuncture points were prepared with 70% alcohol pads with participants in a resting position appropriate for the manipulation of the selected acupoints. Acupuncture procedures were performed by an experienced acupuncturist, using two disposable stainless steel needles (0.3 mm diameter, 25 mm length, Suzhou Jiangsu, China) that were inserted to a depth of 0.3-1 cm according to TCM standards. The sensation of ache or heaviness in the area surrounding the inserted needle (known as "De qi") was always achieved. Treatments lasted 30 minutes and the last 15 minutes were performed by rotating the needle in all of the patients in order to achieve "De qi". Both ear and body acupuncture was performed. The points used were Governing Vessel20 (GV20), Gall Bladder14 (GB14) (x2), Bladder2 (BL2) (x2), BL10 (x2) Yintang in the head; the dominant side of the ear, cervical (C) vertebra C5, antidepression, prostaglandin E1 (PGE1), and body points were Large Intestine4 (Li4) (x2), Li 11 (x2), Stomach36 (ST36) (x2), Liver 3 (Liv3) (x2) (Figure 2).

Serotonin levels were measured in both groups. Fasting venous blood samples were collected by venipuncture into K3 EDTA vacationer tubes (BD). Ten milligram EDTA and 75 mg ascorbic acid was added to all samples and immediately centrifuged at 150 g for 20 minutes. Platelet-rich plasma was separated and frozen at -80 °C until analyses. Serotonin measurements were performed with a microELISA method using a DMN 9602G microELISA microplate reader (Geeing Biotechnology Co., Ltd. China) according to the instruction manual. Blood samples were taken before acupuncture and three months after therapy. All patients were put on a tryptophan restricted diet (poor of bananas, prunes, walnuts, and coffee) and medications that could affect tryptophan levels such as, acetaminophen, catecholamines and reserpine group of drugs for a period of one week before blood collections. In this randomized, controlled, prospective study, patients were informed about side effects of the drug and acupuncture.

Figure 2. Applied acupuncture points: Antihistaminic, C5, PGE1, and antidepression points in the ear; BL2, at the medial end of the eyebrow; BL10, under the external occipital protuberance, 1.3 cun of the lateral; GB14, on the forehead, along the vertical line of the pupil when looking straight ahead; GV20, on the sagittal axis cephalic; LI4, at the midpoint of the second metacarpal bone; LI 11-midway between the lateral side of the transverse crease of the elbow and the epicondyle of the humerus; ST36; edge of tibia; LR3; On the dorsum of foot; between the heads of the first and second metatarsal bones; Yintang; Extraordinary point. C5: Cervical 5; PGE1: ProstaglandinE1; BL2: Bladder2; GB14: Gall Bladder14; GV20: Governing Vessel20; LI4: Large Intestine4; ST 36: Stomach36.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 11.5 software (SPSS Inc., Chicago, IL, USA). Mean, standard deviation, frequency and percentage values were used in the given descriptive statistics of the data. The distribution of the variables was measured with Kolmogorov-Smirnov test. ANOVA (Turkey test) and independent sample t-test were used for the analysis of quantitative data. Paired samples t-test was used in the analyses of the repeated measures. Chi-square test was used for the analysis of qualitative data and Fisher's exact test was used when chi-square test conditions were not met. The results were evaluated in 95% confidence interval, where p<0.05.

RESULTS

Age, sex and education levels between the two groups were similar (Table 1). Aura was present in 14 patients (48.28%) in the acupuncture group, and in 11 in the drug treatment group (p=0.753). Unilateral headache was present in 21 patients in the acupuncture group (72.41%) and 22 patients in the drug treatment group (88%), respectively (p=0.156). Photophobia was also present in 27 patients (93.10%) in the acupuncture group and 25 patients in the drug treatment group (100%), respectively (p=0.181). Photophobia in the acupuncture group was present in 26 patients (89.66%) and in the drug treatment group in 22 patients (88%) (p=0.847). Allodynia was present in 21 patients in the acupuncture group (72.41%) and in 16 patients in the drug treatment group (64%), respectively (p=0.507).

No statistically significant difference was observed between acupuncture and drug therapy groups in mean analgesic drug usage and VAS and MIDAS values before the study (p>0.05). Significantly lower mean analgesic use during study was found in both the acupuncture and the drug treatment groups when compared to the same duration before study (p<0.001 and p<0.001, respectively). The number and

duration of attacks was found to be significantly lower (p<0.001) in the acupuncture and drug treatment groups compared to the values obtained before treatment. Also significantly lower mean VAS values were observed after therapy when compared to values before therapy in the acupuncture and the drug treatment groups, (p<0.001 and p<0.001, respectively). Similarly, mean MIDAS values were found to be significantly lower after therapy in comparison to before therapy in the acupuncture and the drug treatment groups (p<0.001 and p≤0.001, respectively) (Table 2). The mean serotonin values after treatment of the control group (378.52±67.40 ng/mL) were found to be statistically higher (p<0.001) when compared to the acupuncture (314.3±51.54 ng/mL) and the drug treatment group (257.19±12.62 ng/mL). Serotonin levels in the acupuncture and the drug treatment group were found to be significantly higher than the levels measured before treatment (p<0.001) (Table 3).

DISCUSSION

Migraine is a chronic neurological disorder, characterized by mild to severe pulsating headache attacks, often on one side of the head. Diagnosis criteria have been determined by HIS. Migraine is probably 2-3 times more prevalent in women, possibly due to genetic and hormonal reasons. It is classified into two categories as migraine with and without aura. Migraine without aura accounts for approximately 90% of all migraine cases.[9] Based on the pathophysiology of migraine, it is believed that the neurotransmitter serotonin (5-HT) is involved in the initiation of the pain in migraine. The biochemical theory depends on a decrease of serotonin level in blood and increase of 5-hydroxyindolacetic acid (5-HIAA), a metabolite shown in urine during an attack.[10] The effects on migraine exhibited by medicines such as selective serotonin reuptake inhibitors (SSRI) and serotonin receptor antagonists that affect central serotonin transmission are evidence that supports this biochemical theory.[11] In a recent study the effectiveness of a serotonin and noradrenaline reuptake inhibitor (SNRI) such as

Table 1. Patients' demographic features

	Control group			Acupuncture group			Drug group			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	p
Age (years)			30.31±7.4			33.76±7.82			32.04±9.13	0.274
Sex										0.708
Female	22	75.90		24	82.80		21	84		
Male	7	24.10		5	17.20		4	16		

SD: Standard deviation.

Table 2. Clinical characteristics of the patients before and after treatment

	Acupuncture group		Drug group		
	Mean±SD	p	Mean±SD	p	p
Number of attacks (month)					
Before treatment	5.31±1.67		6.2±2.2		=0.098
After treatment	2.07±1.46		1.8±1.41		=0.497
p		<0.001		<0.001	
Attack length (hour)					
Before treatment	26.48±17.56		20.96±13.46		=0.206
After treatment	9.39±11.3		6.28±7.26		=0.245
p		<0.001		<0.001	
Days with headache (month)					
Before treatment	6.86±2.33		6.88±1.94		=0.976
After treatment	2.32±1.79		1.8±1.41		=0.248
p		<0.001		<0.001	
Number of analgesic (month)					
Before treatment	7.03±3.18		5.64±3.15		=0.112
After treatment	1.93±1.72		1.44±1.29		=0.252
p		<0.001		<0.001	
Triptan number (month)					
Before treatment	1.72±2.15		1.4±2.35		=0.599
After treatment	0.39±0.96		0.48±1.3		=0.780
p		<0.001		=0.015	
Visual analog scale					
Before treatment	9.1±0.9		8.88±1.05		=0.404
After treatment	5.75±2.03		4.64±2.56		=0.085
p		<0.001		<0.001	
Migraine disability assessment					
Before treatment	44.62±17.21		42.84±15.35		=0.692
After treatment	8.82±12.4		7.04±8.57		=0.550
p		<0.001		<0.001	

SD: Standard deviation.

venlafaxine in migraine prophylaxis was compared to placebo. This prospective study included a total of 60 patients with migraine without aura that were given 75-150 mg of venlafaxine or placebo randomly. Two months later the effectiveness was evaluated. The results of the study indicated that venlafaxine was more effective compared to placebo in migraine prophylaxis and considered a well-tolerated drug.[12]

In another study conducted to investigate the effectiveness of venlafaxine and amitriptyline in migraine prophylaxis, both were found to be significantly effective in reducing pain parameters but the side effect profile of venlafaxine was found superior when compared to that of amitriptyline.[13] Similar to the results of this study, our study recorded a decrease in pain intensity, frequency and duration

Table 3. Serotonin levels in the group before and after treatment

Tukey multiple comparison test	Serotonin levels (ng/mL) Pre-treatment		Serotonin levels (ng/mL) Post-treatment	
	Mean±SD	p	Mean±SD	p
Control group	378.52±67.40		378.52±67.40	
Acupuncture group	314.3±51.54		314.3±51.54	
p		<0.001		<0.001
Control group	378.52±67.40		378.52±67.40	
Drug group	292.96±36.31		257.19±12.62	
p		<0.001		<0.001
Acupuncture group	292.96±36.31		314.3±51.54	
Drug group	247.14±13.81		257.19±12.62	
p		0.906		<0.001

SD: Standard deviation.

after venlafaxine intake (75-225 mg/day). In addition to the design of the previous studies which included only drug administration, we added the acupuncture group. We compared the effects of both applications upon blood serotonin levels.

Acupuncture is one of the oldest standardized neuromodulatory treatment modalities of traditional Chinese medicine. It is increasingly being adopted in the West as a complementary and alternative treatment to prevent migraine attacks and to relieve pain during migraine.[14] Acupuncture treatment involves the insertion of fine, single-use, sterile needles in acupoints according to a system of channels and meridians. The needles are stimulated by manual manipulation, electrical stimulation or heat. The general theory of acupuncture is based on the premise that there are patterns of energy flow (Qi) through the body that are essential for health. Disruptions of this flow are believed to be responsible for disease.[15] The immersion of the acupuncture needle results in the release of endogenous opioids by stimulating the free nerve endings of pain receptors known to be involved in pain control. Neurotransmitters involved in the analgesic system such as beta-endorphin, serotonin and enkephalin play an important role in this mechanism.[16]

The possibility that acupuncture affects the reward system pathway of the brain by activation of serotoninergic neurons has been suggested by several authors. The latest Cochrane meta-analysis suggests that acupuncture as a migraine prophylaxis is safe and at least as effective, if not more effective than prophylactic drug treatment.[17] Acupuncture's efficiency as a treatment modality has been accepted by the World Health Organization too.

In 22 meta-analysis, a total of 4,419 patients were examined; in six of the studies, 3-4 months of acupuncture have shown to be effective in the treatment of migraine attacks, in 14 studies real and sham acupuncture were compared and acupuncture was found to be the more effective of the two, but in both cases, headache frequency decreased after treatment, in the remaining four studies drug therapy was compared to acupuncture and acupuncture was found to be more effective and to have less side effects than drug therapy.[18]

In two large studies acupuncture treatment was found to be statistically significantly effective in terms of reducing the number of headache days and pain severity in the short-term (three months).[4]

In a study related to migraine, acupuncture and prophylactic drug treatment were compared. A decrease in pain score, increase in serotonin levels and fewer side effects were observed in the acupuncture group.[4] In another remarkable study, acupuncture and valproate treatment were compared and in the group treated with valproate pain severity was decreased and in the acupuncture group no side effect were observed.[19]

Therefore, acupuncture therapy seems to have independent therapeutic effects superior to sham acupuncture, particularly in term of pain relief. There is significant evidence of acupuncture's value, which will expand its use into conventional medicine and encourage further studies of its physiology and clinical value. The treatment process with acupuncture and its efficacy in the short-term after treatment are well known. Long-term effects of treatment need further studies.

The treatment protocol that we applied in our study led to a decrease in the number of migraine attacks, mean attack duration, number of headache days within a month, drug consumption, decrease in VAS, MIDAS values, increase in blood serotonin level. Although, there was no difference in terms of efficacy between the two groups, given the cost and drug side effects of the medications, we think acupuncture is a good alternative treatment.

Studies on the effect of acupuncture on serotonin levels in the treatment of migraine are limited. Two new studies investigating the blood serotonin level in treatment of migraine with acupuncture indicated high serotonin levels. Changes in blood serotonin levels in patients with migraine headaches before and after a course of reflexotherapy.[20]

In another study the use of antidepressants in the treatment of chronic migraine was not associated with changes in serotonin levels, but it has been shown to be more effective in the management of acute pain.[21] To date there is no such data for venlafaxine.

In our study, the serotonin levels of the control group was significantly higher before and after treatment in both the acupuncture and the medication groups.

In conclusion, our study has shown us that, acupuncture is a reliable, inexpensive alternative treatment to venfloxasin in terms of decreasing severity, duration of pain and number of attacks. Long-term studies that include a larger group of

patients are needed to answer the question of whether acupuncture can be an alternative to drug therapy.

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