Evaluation of the Effectiveness of Auricular Acupuncture in Suicidal Ideation and Cortisol Level in Dysthymic Patients with Comorbid Opiate Use Disorders Enrolled in Methadone Maintenance Treatment: A Randomized, Double-Blind, Sham-Controlled Trial

Bijan Pirnia1,2,*, Ali Reza Mohammadi 3, Alireza Zahiroddin 4, Negin Mohammadzadeh Bazargan 3, Parastoo Malekanmehr 5 and Kambiz Pirnia 6

1Department of Psychology, Faculty of Humanities, University of Science and Culture, Tehran, Iran
2Behavioral Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3Islamic Azad University, Science and Research Branch of Tehran, Tehran, Iran
4Department of Psychiatry, Behavior Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5Islamic Azad University Branch of Hamedan, Hamedan, Iran
6Bijan Center for Substance Abuse Treatment, Tehran, Iran

*Corresponding author: PhD Student of Clinical Psychology, Department of Psychology, Faculty of Humanities, University of Science and Culture, Tehran, Iran. Tel: +98-2208450, Fax: +98-2208451, Email: b.pirnia@usc.ac.ir

Received 2017 May 03; Revised 2019 April 06; Accepted 2019 May 11.

Abstract

Background: Suicide is one of the leading causes of death around the world. The hypothalamic-pituitary-adrenal (HPA) axis disorder is involved in the pathophysiology of suicidal behavior. Acupuncture by regulating the activity of the HPA axis could regulate the secretion of cortisol.

Objectives: This study aimed to evaluate the effectiveness of auricular acupuncture in the reduction of cortisol level and suicidal ideation in dysthymic patients with comorbid opiate use disorders enrolled in methadone maintenance treatment (MMT).

Methods: In a randomized, double-blind, sham-controlled trial (TCTR20180328001), from December 2015 to June 2016, 24 patients (mean age = 24 years) with persistent depressive disorder (dysthymia) under methadone maintenance treatment who referred to Bijan Center for Substance Abuse Treatment in Tehran were selected through respondent-driven sampling (RDS). After 28 days of evaluation, the participants were randomized into two active or sham continuous groups. Auricular acupuncture was performed twice a week for four weeks for the experimental group while the control group received the sham acupuncture. Assessments were carried out before treatment (baseline) and every week for four weeks. Salivary cortisol was considered the primary outcome and the suicide ideation was the secondary outcome. The data were analyzed by the generalized estimation equation (GEE) model and the chi-square test. The qualitative data were analyzed using ATLAS/TI 5 software.

Results: Acupuncture had a significant effect on the cortisol level, as the primary outcome, during the four weeks of treatment. Moreover, there was a significant reduction in suicidal ideation as the secondary outcome (all P values < 0.01).

Conclusions: Acupuncture as an alternative method could reduce the cortisol level and significantly decrease suicidal ideation.

Keywords: Acupuncture, Suicidal Ideation, Methadone, Cortisol, Depression

1. Background

Suicide is one of the leading causes of death accounting for 1.5% of all deaths worldwide. It has a considerable frequency among patients with depressive disorder (1). On the other hand, the suicide rate is several times higher in patients treated with methadone than in the general population (2).

According to the theory of neural plasticity, irregularities of the hypothalamic-pituitary-adrenal (HPA) axis leads to depression symptoms and could be involved in the pathophysiology of suicidal behavior. Oscillation or high-level cortisol has been reported in suicide attempters (1, 3).

On the other hand, discontinuing the use of substances is associated with psychological effects more harmful than its physical consequences. The Post-Acute Withdrawal Syndrome (PAWS) is a set of sustained injuries occurring after discontinuing the use of substances such as alcohol, opioids, benzodiazepines, and stimulants.
Acupuncture is a complementary medicine first described in 2,500 BC (4). The National Acupuncture Detoxification Association (NADA) has developed a protocol for auricular acupuncture.

Acupuncture has been associated with the regulation of HPA activity and adrenocorticotropic hormone (5). In this regard, Pirnia et al. (6) showed the significant effect of acupuncture on the level of salivary cortisol in a patient with colon cancer. Moreover, the results of another study by Pirnia et al. (7) showed that acupuncture is associated with the reduction of symptoms based on the addiction severity index (ASI).

The study of Tanahashi et al. (8) also showed that the use of acupuncture is associated with alleviated symptoms of mild depression by improved HPA axis function. Studies show that acupuncture reduces depression symptoms in human and animal models (9, 10). The results of a study by Pirnia et al. (11) indicated that acupuncture was associated with reductions in cortisol and depression levels in depressed patients.

Contrary to these findings, a study by Pirnia et al. (12) showed acupuncture had no significant effect on the decrease of subsyndromal depression among methamphetamine users. Moreover, the results of a study by Pirnia and Pirnia (13) showed that acupuncture was not associated with the reduced depression index in a case with lobular carcinoma.

2. Objectives

Due to the conflicting findings of the effectiveness of acupuncture and the importance of biological markers such as cortisol in the pathophysiologic understanding of psychiatric disorders, this study examined the following question: could acupuncture be effective in the regulation of salivary cortisol levels by improving HPA axis function, as well as in the reduction of suicidal ideation?

3. Materials and Methods

This randomized, double-blind, sham-controlled trial was conducted at Bijan Center for Substance Abuse Treatment in Tehran, Iran. The data were collected from December 2015 to June 2016.

The inclusion criteria were (1) age of 18-65 years, (2) ongoing patient status at the addiction clinic, (3) methadone intake for at least two years (syrup, mean ± SD = 35 ± 0.3 cc/per day), (4) screening based on scores within two standard deviations on the suicidal ideation scale of Beck and the diagnosis of persistent depressive disorder (dysthymia) based on diagnostic interviews and the adoption of DSM-5 criteria (since the minimum period for avoiding opioids other than methadone was considered two years, dysthymia symptoms after complete abstinence are short-term and are different from the diagnosis of mood disorders without a history of substance use), and (5) the history of at least one episode of suicide planning or committing.

The exclusion criteria included (1) nickel-allergy, (2) ear infection, (3) heart disease, (4) taking any psychiatric medication, and (5) receiving psychological interventions within the three months leading up to the study. In this study, concerning the one-way direction test and the assumptions of $Z = 1.645$, $d = 0.2$, $\alpha = 0.05$, and the test power of $1 - \beta = 0.84$, the sample size was estimated at 24 people. The sample was selected through respondent-driven sampling (RDS). The randomization sequence was computer-generated, with the randomization itself conducting using SPSS 20 software (random number generation) (SPSS, Inc., Chicago, IL, USA). The statistical significance was accepted at the level of $P < 0.05$. The allocation concealment was done by the researcher who was responsible for the randomization.

Acupuncture was performed twice a week for four weeks (eight sessions) in both ears using disposable stainless steel needles (0.25 + 13 mm) with a depth of 2 - 3 mm and using manual stimulation. Participants in the sham group also received eight sessions of acupuncture treatment; however, needling was performed 1 cm away from the real acupuncture points.

Cortisol was evaluated in the form of three meals on a randomly selected day every week and the mean of the three measures was considered as a criterion. Cortisol was collected from the saliva into labeled tubes. The patients were taught about eating, brushing the teeth, or any drink (except water) in hours prior to the testing session. The cortisol samples were stored at $\leq -20^\circ$C and analyzed by enzyme-linked immunosorbent assay kit (ELISA).

Data collection was conducted using structured clinical interviews, a researcher-made demographic questionnaire, the suicide scale, and the radioimmunoassay method. The structured clinical interview for DSM-5 (SCID) was used for the diagnosis of dysthymia disorder based on DSM-5. A researcher-made demographic questionnaire was used by the researcher to collect personal information. The Beck scale for suicidal ideation (BSSI) is a 21-item scale to assess the severity of ideation and planning to commit suicide during the past seven days. Cronbach’s alpha of this scale was calculated in the range of 0.81 to 0.91. The validity of the Persian version of this scale was estimated at 0.95 (14). Radioimmunoassay (RIA) is a tool widely used at medical laboratories. In this method, radioactive iodine is used to create signals. Urinalysis was performed to ensure that the patients adhered to the maintenance treatment.
Pirnia B et al.

urine test with the threshold of > 300 ng/mL was done for each participant weekly and randomly (3).

According to the results of the Kolmogorov-Smirnov test related to the non-normal distribution of the two variables, the generalized estimation equation test was used. The chi-square test was used to evaluate the demographic characteristics.

After completing the explanation of the study details, written informed consent was obtained from eligible patients in their native language (Persian). Patients received only treatment routine-centered treatment. All stages of the study were performed after obtaining informed consent from patients and based on the latest version of the Helsinki Declaration. This trial was registered at www.clinicaltrials.in.th (TCTR20180328001, ethical approval: IR.SBMU.RETECH.REC.1397.631).

4. Results

The two groups were compared in terms of marital status, education level, employment status, monthly income, age, and ethnicity (Table 1). The results showed there was a difference in the distribution of employment status in the acupuncture group and monthly income in the sham group based on the chi-square test.

The urinalysis results showed all participants adhered to the methadone maintenance treatment (MMT).

The groups were compared in the salivary cortisol level (Table 2). The results of the salivary cortisol level showed significant differences between the experimental and sham groups at weeks five, six, seven, and eight.

The two groups were compared in suicidal ideation, as well (Table 3). The results of the suicidal ideation test scores showed significant differences between the experimental and control groups at weeks six, seven, and eight.

5. Discussion

Suicide is the second leading cause of death in young men and suicidal behaviors are mostly occur in psychiatric patients, especially patients with depressive disorders (1). It seems that one of the underlying mechanisms of depression is the HPA axis (8). The HPA axis dysfunction can be reflected in the levels of cortisol (3) so that high levels of cortisol have been reported in suicide attempters with depression (2).

In this randomized, double-blind, sham-controlled trial, we investigated the effectiveness of auricular acupuncture in suicidal ideation and cortisol level in dysthymic patients under methadone maintenance treatment. The results showed that four weeks of acupuncture treatment decreased the salivary cortisol level as the primary outcome and suicidal ideation as the secondary outcome. Consistent with the results of the primary outcome in the present study, Pirnia et al. (6) reported that the use of acupuncture leads to the regulation of HPA axis activity in a case with colon cancer. Guo et al. (5) showed that acupuncture has a significant effect on the level of morning salivary cortisol. In line with our findings, Yao et al. (15) demonstrated that acupuncture could have a moderating effect on HPA axis activity and influenced the cortisol levels. The study by Zhu et al. (16) showed that the use of electro-acupuncture could improve HPA axis hyperactivity in mice through AVP signaling.

In addition, the results of a study by Pirnia et al. (11) indicated that acupuncture was associated with reduced cortisol and depression levels in depressed patients under methadone maintenance treatment.

In fact, acupuncture can stimulate the secretion of ty-
Table 2. The Results of the Generalized Estimating Equation in the Variable of Salivary Cortisol Level

| Course/Weeks | Salivary Cortisol | Pairwise Comparisons |
|--------------|------------------|----------------------|
|              | Experimental     | Sham Group           |                     |
| Baseline     |                  |                      |                     |
| Week 1       | 181 (36)         | 182 (41)             | NS                   |
| Week 2       | 182 (66)         | 183 (52)             | NS                   |
| Week 3       | 183 (39)         | 182 (64)             | NS                   |
| Week 4       | 182 (51)         | 181 (54)             | NS                   |
| Treatment    |                  |                      |                     |
| Week 5       | 178 (68)         | 182 (52)             | 0.047<sup>a</sup>   |
| Week 6       | 178 (47)         | 183 (61)             | 0.041<sup>b</sup>   |
| Week 7       | 176 (67)         | 182 (49)             | 0.009<sup>b</sup>   |
| Week 8       | 175 (53)         | 183 (69)             | 0.006<sup>b</sup>   |

<sup>a</sup>P < 0.05.  
<sup>b</sup>P < 0.01.

Table 3. The Results of the Generalized Estimating Equation in the Variable of Suicidal Ideation

| Course/Weeks | Suicidal Ideation | Pairwise Comparisons |
|--------------|-------------------|----------------------|
|              | Experimental      | Sham Group           |                     |
| Baseline     |                   |                      |                     |
| Week 1       | 11.23 (1.14)      | 11.42 (1.73)         | NS                   |
| Week 2       | 12.01 (0.94)      | 11.85 (1.12)         | NS                   |
| Week 3       | 11.84 (1.24)      | 12.22 (2.06)         | NS                   |
| Week 4       | 12.11 (1.03)      | 11.57 (1.42)         | NS                   |
| Treatment    |                   |                      |                     |
| Week 5       | 11.06 (1.63)      | 11.84 (1.53)         | NS                   |
| Week 6       | 10.64 (1.12)      | 11.82 (1.09)         | 0.04<sup>a</sup>    |
| Week 7       | 10.32 (1.13)      | 11.48 (2.11)         | 0.04<sup>a</sup>    |
| Week 8       | 10.38 (0.85)      | 11.94 (1.21)         | 0.01<sup>b</sup>    |

<sup>a</sup>P < 0.05.  
<sup>b</sup>P < 0.01.

rosine hydroxylase, increase the levels of dopamine, and reduce stress hormones such as cortisol, ultimately leading to the feeling of well-being (11).

This study showed that acupuncture could reduce the severity of suicidal ideation, as well. In line with our findings, the results of a study by Molinoff (9) indicated that acupuncture could be used as a preventive method for suicidal ideas. Moreover, several studies have investigated the effectiveness of acupuncture in depression symptoms.

The results of a study on mice showed that mechanical acupuncture instrument (MAI) increased the effects of antidepressants and reduced the symptoms of depression (10).

The results of a study by Le et al. (17) demonstrated that electro-acupuncture was associated with the reduced symptoms of depression by modulating HPA axis function and enhancing the activity of the hippocampus. In a study, Han et al. (18) stated that acupuncture caused a significant decrease in the symptoms of depression by regulating the biological flow. The results of a meta-analysis of 18 randomized clinical trials showed that acupuncture could be used for improving depression related to insomnia (19).

The results of a study by Pirnia et al. (7) on the effectiveness of acupuncture in the reduction of addiction indices, including the addiction severity index, indicated the significance of acupuncture intervention.

Contrary to the results of this study, the study by Pirnia et al. (7) showed that acupuncture had no significant effect on the improvement of psychological indices, including pain relief in a patient with Trismus syndrome. The difference between the present study and the study by Pirnia et al. (7) is in the history of methamphetamine abuse in the patient with Trismus. The results of previous studies showed that the production of tyrosine hydroxylase as a precursor to producing dopamine in chronic methamphetamine users could have an important role in the effectiveness of acupuncture (20).

The findings of this study showed that acupuncture could be an alternative to medication and psychotherapy for reducing suicidal ideation and improving HPA axis function by modulating cortisol secretion.

This study had some limitations. Concerning the limitations of research in the field of addiction, the sample of the study only consisted of men undergoing methadone maintenance. The evaluation of the role of tyrosine hydroxylase as a mediator in the effectiveness of acupuncture can be interesting in future studies.

5.1. Conclusions

The results of the study showed that acupuncture as an alternative therapy could reduce the cortisol level and significantly reduce suicidal ideation. The results of this study support the usefulness of cortisol level as a factor influencing suicide.

Footnotes

**Authors’ Contribution:** Bijan Pirnia, Kambiz Pirnia and Alireza Zahiariodin designed and performed the study. Bijan Pirnia, Negin Mohammazadeh Bazargan, and Ali Reza Mohammad assisted with data analysis and interpretation of findings. Parastoo Malekanmehr and Bijan Pirnia
References

1. Moica T, Grecu IG, Moica S, Grecu MG, Buicu GE. Cortisol and hippocampal volume as predictors of active suicidal behavior in major depressive disorder: Case report. Balkan Med J. 2016;33(6):706-8. doi: 10.552/balkanmedj.2016.150842. [PubMed: 27994930]. [PubMed Central: PMC5156456].

2. Michel L, Lions C, Maradan G, Mora M, Marcellin F, Morel A, et al. Suicidal risk among patients enrolled in methadone maintenance treatment: HCV status and implications for suicide prevention (ANRS Methaville). Compr Psychiatry. 2015;62:123-31. doi: 10.1016/j.comppsych.2015.07.004. [PubMed: 2634476].

3. Pirnia B, Givi F, Roshan R, Pirnia K, Soleimani AA. The cortisol level and its relationship with depression, stress and anxiety indices in chronic methamphetamine-dependent patients and normal individuals undergoing inguinal hernia surgery. Med J Islam Repub Iran. 2016;30:395. [PubMed: 27579281]. [PubMed Central: PMC5004567].

4. Eshevari L. Acupuncture and chronic pain management. Annu Rev Nurs Res. 2017;35(1):111-34. doi: 10.1146/annurev-nurs-052916-124100. [PubMed: 27935777].

5. Guo J, Huang W, Tang CY, Wang GL, Zhang F, Wang LP. Effect of acupuncture on sleep quality and hyperarousal state in patients with primary insomnia: Study protocol for a randomised controlled trial. BMJ Open. 2016;6(3). e009594. doi: 10.1136/bmjopen-2015-009594. [PubMed: 26956606]. [PubMed Central: PMC478533].

6. Pirnia B, Pirnia K, Soleimani AA, Kolahi P. Acupuncture for back pain in colon cancer: A case report. Int J Cancer Manag. 2017;10(12). doi: 10.5812/ijcm.15087.

7. Pirnia B, Najafi E, Soleimani AA, Malekannemehr P, Pirnia K. The effectiveness of acupuncture on addiction severity index, a single case experimental design in a case of methamphetamine abuser patient with trismus syndrome. Crescent J Med Biol Sci. 2018;5(3):265-7.

8. Tanahashi N, Takagi K, Amagasu N, Wang G, Mizuno K, Kawaguchi J, et al. Effect of acupuncture stimulation on rats with depression induced by water-immersion stress. Neurosci Lett. 2016;618:99-103. doi: 10.1016/j.neulet.2016.02.051. [PubMed: 26940421].

9. Molinoff M. Mental crisis acupuncture relief. Raleigh acupuncture. Suicide prevention tool. Raleigh Acupuncture Associates; 2018.

10. Seo SY, Moon JY, Kang SY, Kwon OS, Kwon S, Bang SK, et al. An estradiol-independent BDNF-NPY cascade is involved in the antidepressant effect of mechanical acupuncture instruments in ovariecotomized rats. Sci Rep. 2018;8(1):5849. doi: 10.1038/s41598-018-23824-2. [PubMed: 29643431]. [PubMed Central: PMC5895799].

11. Pirnia B, Pirnia K, Mohammadpour S, Malekannemehr P, Soleimani A, Mahmoodi Z, et al. The effectiveness of acupuncture on HPA functional in depressed patients under methadone maintenance treatment, a randomized double-blind sham-controlled trial. Asian J Psychiatr. 2018;36:62-3. doi: 10.1016/j.ajp.2018.06.008. [PubMed: 2996889].

12. Pirnia B, Pirnia K, Bazyari K, Aslani F, Malekannemehr P. Physical or psychological therapy? Cognitive behavioral therapy or acupuncture for subsyndromal depression among methamphetamine users. Iran J Public Health. 2019. doi: 10.4103/ijph.IJPH.15083.

13. Pirnia B, Pirnia K. Comparison of two mindfulness-based cognitive therapies and acupuncture on the pain and depression index in a case with lobular carcinoma: A single case experimental study. Int J Cancer Manag. 2018;11(6). doi: 10.5812/ijcm.65641.

14. Khorosavnı V, Mohammadzadeh A, Sharifi Bastan F, Amirinezhad A, Amini M. Early maladaptive schemas and suicidal risk in patients with bipolar disorder. Psychiatry Res. 2019;271:95-5. doi: 10.1016/j.psychres.2018.11.067. [PubMed: 3052918].

15. Yao H, Wei D, Cai D, Yu S, Zhang C, Wei J, et al. [Effects of acupuncture on ANP and CNP in adrenal gland and CORT in plasma in rats with chronic emotional stress anxiety]. Zhongguo Zhen Jiu. 2016;36(2):69-74. Chinese. [PubMed: 27349820].

16. Zhu J, Chen Z, Zhu L, Meng Z, Wu G, Tian Z. Arginine vasopressin and arginine vasopressin receptor 1b involved in electroacupuncture-attenuated hypothalamic-pituitary-adrenal axis hyperactivity in hepatectomy rats. Neuro modulation. 2016;19(5):496-506. doi: 10.1111/ner.12366. [PubMed: 26573696]. [PubMed Central: PMC5061097].

17. Le J, Yi T, Qi L, Li J, Shao L, Dong JC. Electroacupuncture regulate hypothalamic-pituitary-adrenal axis and enhance hippocampal serotonin system in a rat model of depression. Neurosci Lett. 2016;615:66-71. doi: 10.1016/j.neulet.2016.01.004. [PubMed: 2673866].

18. Han CH, Wang HS, Lee YJ, Lee SN, Abanes J, Lee BH. Chronic depression treated successfully with novel tapping therapy: A new approach to the treatment of depression. Neuropsychiatr Dis Treat. 2016;12:2281-6. doi: 10.2147/NPDT.S17535. [PubMed: 27330295]. [PubMed Central: PMC4898438].

19. Dong B, Chen Z, Yin X, Li D, Ma J, Jin Y, Pan P, et al. The efficacity of acupuncture for treating depression-related insomnia compared with a control group: A systematic review and meta-analysis. Biomed Res Int. 2017;2017:9614810. doi: 10.1155/2017/9614810. [PubMed: 2828677]. [PubMed Central: PMC532966].

20. Pirnia B, Nakhost HR, Pirnia K, Moradi AR, Teimouri M. Ear acupuncture in treating trismus-syndrome: A case report. Ann Med Health Sci Res. 2017.