

# The Effectiveness of Acupuncture on Cortisol Levels in a Prostate-Carcinoma Patient under Androgen Deprivation Therapy with Dysthymic Syndrome: A Single-case Experimental Design

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## Abstract

The prevalence of suicide is high in patients with prostate cancer. The hypothalamic–pituitary–adrenal (HPA) axis disorder plays a role in the pathophysiology of depression and suicidal ideation. Acupuncture regulates cortisol secretion through controlling the activity of HPA axis. The purpose of this study was to evaluate the effectiveness of acupuncture on decreasing depression, suicidal ideation, and cortisol secretion in a patient with prostate cancer. In a single-case experimental study, lasting from December 2015 to June 2016, a patient suffering from prostate carcinoma with dysthymic disorder and suicidal ideation was selected through purposive sampling method. Following 30 days of evaluation at baseline, the subject was treated for four weeks with auricular acupuncture along with the usual treatment. The results were analyzed by generalized estimation equation (GEE) and Repeated Measures Correlation (rmcorr) through statistical package for the social sciences (SPSS) software version 22. The primary outcomes showed that acupuncture had a significant effect on reducing depression index, suicidal ideation, and cortisol levels during the treatment process (all  $P$  values < 0.05). Secondary outcomes further showed that a significant positive correlation existed between depression, suicidal ideation, and salivary cortisol levels (all  $P$  values < 0.05). The findings of this study showed that auricular acupuncture can replace medication and psychotherapy to reduce depression and suicidal ideation and regulate HPA-axis function through modulating the cortisol secretion. However, this conclusion requires more high-quality randomized clinical trials.

**Keywords:** Auricular acupuncture, Suicidal ideation, Cortisol, Prostate cancer, Androgen deprivation therapy

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## Introduction

Prostate cancer is one of the most common malignancies among men, accounting for 19% of cancers and is the third leading cause of cancer mortality. Patients with prostate cancer are prone to depression and suicidal ideation.<sup>1</sup> Depression syndromes and suicidal ideation usually observed following cancer diagnosis or hospitalization for treatment. Accounting for 1.5% of all deaths, suicide is yet another cause of death worldwide.<sup>1</sup> Suicide has a high frequency among patients with depressive disorders. Research has shown that there is a significant relationship between depression and suicidal ideation in cancer patients. Meanwhile, the reduction in serum testosterone levels due to androgen deprivation therapy causes several side-effects such as impairment in cognitive function, sexual dysfunction, fatigue, reduced sleep quality, and the occurrence of symptoms of anhedonia and depression.<sup>2</sup>

The function of hypothalamic, pituitary, adrenal (HPA) axis, as the core of response to stress, is necessary for adaptation to stimuli from the external environment, while any damage to the function of this axis causes mental disorders. Studies have shown that disorders in HPA axis lead to depression cognitive syndrome and can play a role in the pathophysiology of suicidal behavior.<sup>1</sup> One aspect of dysregulation in HPA axis is the emergence of fluctuations in the cortisol index.<sup>6</sup> High levels of cortisol have been reported in suicidal people with depression.<sup>3</sup> In fact, the dysregulation of HPA axis is known as a potential risk factor for suicide, which is also shown to be associated with blunted cortisol reactivity.<sup>3</sup> Recent evidence further suggests that individuals with a history of suicide attempts exhibit lower levels of cortisol when exposed to acute stress test.<sup>8</sup> The blunted cortisol reactivity, an implication of HPA-axis function dysregulation, is known as a trait marker or phenotype for suicide risk in vulnerable people.<sup>3</sup>

Today, the use of complementary therapies concerning cancer is more welcome by therapists.<sup>4</sup> Acupuncture, with a history of two thousand years, is among the complementary therapies in

medicine. The National Acupuncture Detoxification Association (NADA) is a functional menu for the auricular acupuncture protocol.<sup>4</sup>

Several studies have been conducted on the efficacy of acupuncture on cortisol levels. Acupuncture has been reported to adjust the activity of HPA axis and improve adrenocorticotrophic hormone function and cortisol secretion regulation.<sup>5</sup> Studies have shown that acupuncture has a significant effect on the level of morning salivary cortisol.<sup>6</sup>

This study was done to investigate the effectiveness of acupuncture on depression, suicidal ideation and cortisol levels in a patient suffering from prostate carcinoma with dysthymic syndrome treated with androgen deprivation therapy. The objective of the present research is based on: a) the controversial results on the effectiveness of acupuncture on psychological indices and the importance of biological markers such as cortisol in the pathophysiological understanding of psychiatric diseases, and b) the higher therapeutic efficacy of a combination of acupuncture and SSRI compared with SSRI therapy alone.<sup>17</sup>

## Case Report

AB design was employed with a multiple baseline (Clinical Trial Registration Code: TCTR20190208001), with A as the baseline phase and B as the intervention phase. Data were collected from December 2015 to June 2016. Through purposive sampling method, we selected a 61-year-old man who was under methadone maintenance treatment, had received radical prostatectomy for prostate localized two years ago, and had undergone androgen deprivation therapy. The patient had three attempts at suicide over the previous 11 months. Two suicide attempts were performed with a high dose of benzodiazepine and the last attempt was made by cutting left hand arteries in the camp. The patient was under treatment as usual (TAU) with degarelix at a dose of 40 mg per day, venlafaxine with a daily dose of 225 mg and methadone syrup (Daru Pakhsh) with a daily dose of 15 mg. The

subject entered the treatment process with a complaint of depression and suicidal ideation.

A preliminary assessment was performed 28 days before the registration of the baseline by a team composed of a neurologist, two clinical psychologists, and a nurse. In this study, a structured clinical interview (SCID), a researcher-made demographic checklist,<sup>18</sup> Beck Depression Inventory (BDI), Beck Scale for Suicidal Ideation (BSSI), and Radioimmunoassay (RIA) were used.

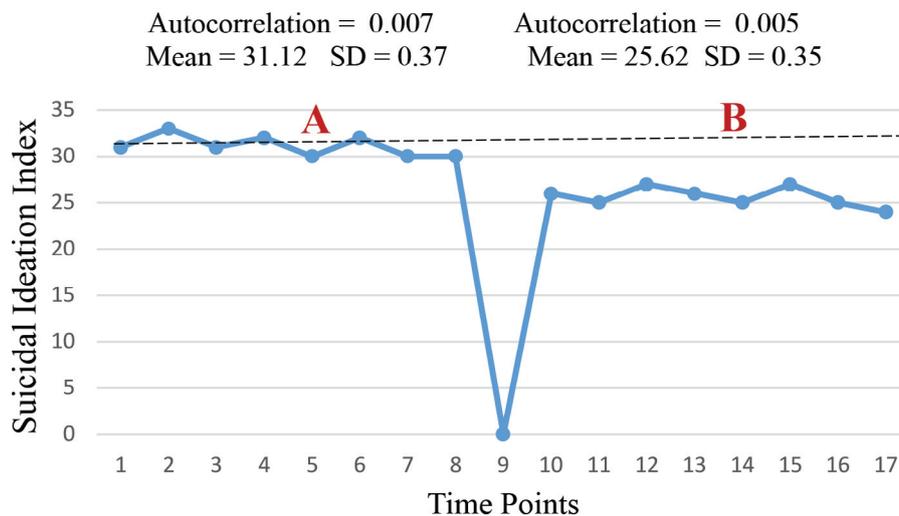
Acupuncture was performed twice a week for four weeks (eight sessions) and the duration of each session, performed before lunch, was 30-45 minutes. During each session, five-ear points, namely Sympathetic, Shen Men, Kidney, Liver and Lungs were interfered. Acupuncture in both ears was performed using one-use stainless steel needles (13 mm + 0.25 mm) with a depth of 2-3 mm by a trained physician and an acupuncturist with a diploma and five-year history of treatment.

Cortisol was randomly sampled twice a week in each of the three meal and the average of the three times of sampling was evaluated as a criterion. Cortisol was collected from saliva via Salvi test. The patient entered his saliva through a small straw into tubes labeled with time and date. The subject was trained on eating, brushing teeth, or drinking any drinks (except water) prior to the testing sessions. All laboratory evaluations

were performed after 11 A.M. (96% between 11 A.M. and 3 P.M.) to avoid the ineffectiveness of the sampling from awakening response cortisol. Cortisol samples were stored at -20 °C or lower until evaluation. Cortisol levels were determined using an Enzyme Linked Immunosorbent Assay (ELISA) kits designed to analyze saliva. Depression indices, suicidal ideation and cortisol levels were evaluated over a period of eight weeks in 16 stages (four weeks of evaluation and four weeks of treatment, measured twice a week). Data were analyzed using generalized estimation equation (GEE) and Repeated Measures Correlation (rmcorr) in SPSS software 22 (SPSS, Inc., Chicago, IL, USA) and the significance criterion was considered as 0.05. All stages of the research were performed after obtaining informed written consent from the patient based on the latest version of the Declaration of Helsinki (DoH).

Distribution of the scores of suicidal ideation during 16 evaluation stages is presented in figure 1.

As shown in figure 1, the suicidal ideation scores have a mean of 31.12 and a standard deviation of 0.37 in the baseline stage and a mean of 25.62 and a standard deviation of 0.35 in the treatment stage. The autocorrelation was further calculated between the measured points as 0.007 at the baseline and 0.005 in treatment. The results



**Figure 1.** Distribution of the scores of suicidal ideation during 16 evaluation stages.

of GEE showed a significant decrease in the suicidal ideation during the treatment process ( $P < 0.05$ ). Moreover, depression scores had a mean and standard deviation of 28.51 and 0.64 and 26.32 and 0.83 in the baseline stage and treatment stage, respectively. The autocorrelation between the measured points was 0.009 in the baseline and 0.008 in the treatment phase. The results of the generalized estimation equation test show a significant decrease in depression during the treatment process ( $P < 0.05$ ).

Distribution of the scores of salivary cortisol levels during 16 evaluation steps is presented in figure 1.

As shown in figure 2, the salivary cortisol levels had a mean and standard deviation of 17.95 and 0.29 and 14.74 and 0.24 in the baseline stage and the treatment stage, respectively. The autocorrelation was further calculated between the measured points as - 0.005 and 0.007 in the baseline and treatment stage, respectively. The results of the GEE test showed a significant decrease in the salivary cortisol levels during the treatment process ( $P < 0.05$ ).

The results of the rmcrr showed that there was a significant positive correlation between depression and suicidal ideation indices and cortisol levels.

( $\text{rrm}(70, \text{Cortisol- Depression}) = 0.64, 95\% \text{ CI } [0.72, 0.56], P < 0.05$ )

( $\text{rrm}(70, \text{Cortisol- Suicidal Ideation}) = 0.58, 95\% \text{ CI } [0.54, 0.62], P < 0.05$ )

## Discussion

In this study, we evaluated the effectiveness of acupuncture on cortisol levels and psychological indicators in a depressed patient with a history of suicidal attempts. The primary outcomes showed that four weeks of acupuncture reduced depression, suicidal ideation, and cortisol secretion. Secondary outcomes further showed a significant positive correlation between depression and suicidal ideation and salivary cortisol levels.

Wei et al.<sup>5</sup> employed acupuncture through promoting adrenocorticotrophic hormone and plasma cortisol secretion which regulated the activity of HPA axis in asthmatic mice, which is in line with the present study. Guo et al.<sup>6</sup> also found that acupuncture had a significant effect on the salivary cortisol levels in the morning. Consistent with our findings, Yao et al.<sup>7</sup> showed that acupuncture had a moderating effect on the activity of HPA axis and the cortisol levels. Moreover, a study by Zhou et al.<sup>8</sup> revealed that the use of electrical acupuncture can improve the hyperactivity of HPA axis through AVP signaling in mice.

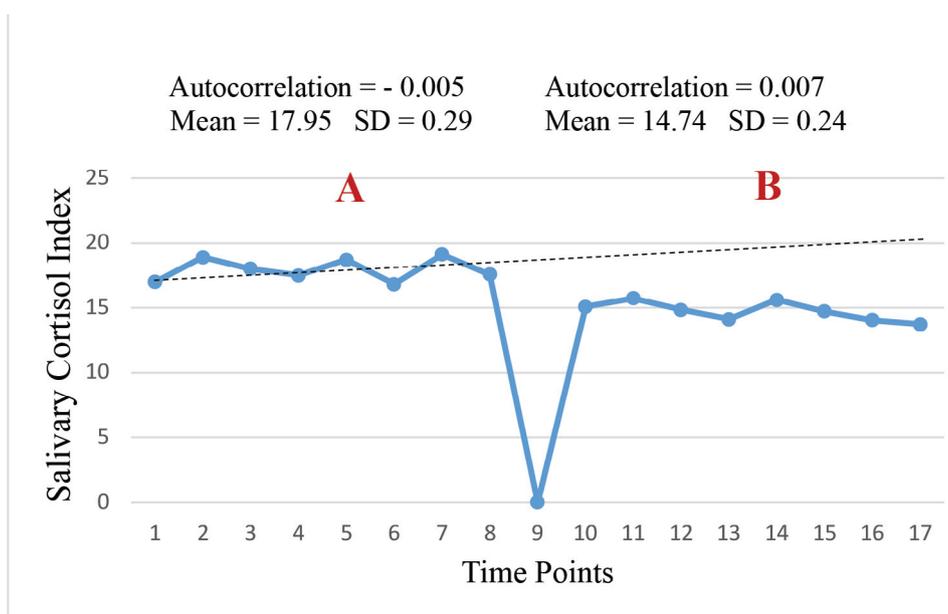


Figure 2. Salivary cortisol levels during 16 evaluation stages.

A part of the findings of the present study showed that acupuncture reduced depression. In accordance with our findings, Pirnia et al.<sup>9</sup> reported that acupuncture induced a significant improvement in depressive symptoms of methamphetamine users. Lee et al.<sup>10</sup> showed that electrical acupuncture reduced the function of HPA axis and increased the activity of hippocampus by reducing depression syndromes, which is also in line with the present research. Lee et al.,<sup>11</sup> also reported that acupuncture, with the regulation of biologic flow, caused a significant decrease in depression syndrome. The results of a meta-analysis including 18 randomized clinical trials showed that acupuncture can be utilized as an alternative therapy for medication to improve the depression related to insomnia.<sup>12</sup> Lee et al.<sup>11</sup> showed that electrical acupuncture decreased mRNA in hypothalamic, plasma cortisol, and depression syndromes through modulating HPA axis in mice with mild depression. Pirnia et al.<sup>4</sup> also proposed the effectiveness of acupuncture on lowering depression and cortisol secretion. HPA axis activity is one of the main mechanisms of depression.<sup>4</sup> Results of a meta-analysis by Zhang et al.<sup>13</sup> corroborated the viewpoint that acupuncture is an effective and safe treatment for depression. The study results of Kim et al.<sup>14</sup> also showed the paucity of conclusive evidence regarding the benefits of acupuncture for the treatment of cancer survivors.

The most important limitation of this study was the single case. Single case studies do not look for generalization of the findings and they are the basis of randomized clinical trials.

## Conclusion

The results of this study showed that acupuncture, as an alternative method, can significantly reduce the cortisol index, depression, and suicidal ideation. Along with the research background, it seems that an underlying mechanism of depression is the activity of HPA axis. Acupuncture can play a neuroprotective role by regulating various mechanisms to improve cognitive dysfunction. These findings can be

applied in the design of neurological, psychological, and neuropsychological interventions. Also, the results of this study support the use of cortisol marker as an effective factor in the suicide process. Future studies can examine the effect of medication on HPA axis in order to manage suicide. Robust randomized controlled studies are warranted to confirm the findings. Also, the study of the relationship between demographic variables and cortisol levels in predicting suicide can be a suitable route for future studies.

## Conflict of Interest

None declared.

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