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The cortisol level and its relationship with depression, stress and anxiety indices in chronic methamphetamine-dependent patients and normal individuals undergoing inguinal hernia surgery

Bijan Pirnia*[1], Fatemeh Givi[2], Rasool Roshan[3], Kambiz Pirnia[4], Ali Akbar Soleimani[5]

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Abstract

Background: Stimulants addition and abuse can cause some functional and morphological changes in the normal function of glands and hormones. Methamphetamine as an addictive stimulant drug affects the Hypothalamic-pituitary-adrenal (HPA) axis and consequently makes some changes in the psychological state of the drug users. The present study aims to examine the relationship between plasma levels of cortisol with depression, stress and anxiety symptoms in chronic methamphetamine-dependent patients and normal individuals who have undergone the inguinal hernia surgery.

Methods: To meet the purpose of the study, 35 chronic methamphetamine-dependent patients in the active phase of drug abuse and 35 non-users (N=70) who were homogenized regarding the demographic features were purposefully selected from among the patients referred to undergo inguinal hernia surgery since March 15 to June 9, 2015. The participants were then divided into the control and experiment group. The changes in cortisol levels in plasma were measured using Radioimmunoassay (RIA) in three-time series including 0 (upon the induction of anesthesia), 12 and 24 hours after the surgery. Further, three behavioral indices of depression, anxiety and stress were measured using the Depression Anxiety Stress Scale 21 (DASS-21) and then the data were analyzed using t-test and Pearson Correlation coefficient.

Results: The plasma level of cortisol in the chronic methamphetamine-dependent patients (experiment group) had a significant increase in 24 hours after surgery ($p<0.05$). This study showed that cortisol levels in chronic methamphetamine-dependent patients were significantly higher than non-dependent patients in response to alarming events such as inguinal surgery. Changes in cortisol levels were intensified due to a confrontation with the phenomenon of pain and anxiety. In addition, depression index was higher in the chronic methamphetamine-dependent patients than that in the non-dependent patients. However, there was no significant relationship between the cortisol level and depression index ($p=0.001$).

Conclusion: The Hypothalamic-pituitary-adrenal (HPA) axis is considered as a key structure in the addiction to simulants, the reason which can explain the faster response of the chronic methamphetamine-dependent patients to the stressors such as surgery.

Keywords: Depression, Cortisol, Hypothalamic, pituitary, adrenal, Methamphetamine, Radioimmunoassay, Surgery, Addiction.

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Introduction

Methamphetamine abuse has increased in recent years. So that, the second place of drug abuse in America is allocated to methamphetamine (Met), and it is estimated that there are over thirty million methamphetamine users worldwide (1). From a neurological point of view, the use of these drugs causes some transgenic epithelial changes in brain structure creating addic-

[1]. (**Corresponding author**) PhD Student of Clinical Psychology, Department of Psychology, Faculty of Humanities, University of Science and Culture, Tehran, Iran. b.pirnia@usc.ac.ir
[2]. MA in Clinical Psychology, Department of Psychology, Islamic Azad University of Rudehen Branch, Tehran, Iran. givi_fatemeh@yahoo.com
[3]. Professor of Psychology, Department of Psychology, Faculty of Humanities, Shahed University, Tehran, Iran. rasolroshan@yahoo.com
[4]. Internal Disease Specialist, Baharloo Hospital, Tehran, Iran. bijanpirnia@usc.ac.ir
[5]. Assistant Professor of Psychology, Department of Psychology, University of Science and Culture, Tehran, Iran. solaymani64@yahoo.com

tive behavior (2). Although the neural circuitry involved in response to stress is not clearly known, most of these changes are observed in hypothalamic-pituitary-adrenal axis (HPA). In fact, the HPA axis plays a crucial role in maintaining homeostasis (3). Methamphetamine increases the activity of the HPA axis (4). New research suggests that the HPA axis will change due to the frequent use of methamphetamine and the stress hormone levels also change during the process of abstinence (5,6). The activation of this axis increases the Adrenocorticotropic Hormone (ACTH). Increased glucocorticoid secretion can be followed by serious consequences, including cell death (4) and induction of regeneration dendritic (7).

In fact, the stress and HPA axis are considered as the key component of addiction to stimulants. In short, stressful stimuli increase the secretion of corticotrophin from the ventricular cells in the hypothalamus which consequently leads to cortisol secretion (8). Stressor factors working through the central and peripheral nervous system will stimulate the HPA axis (9).

These changes include changes in the secretion of stress hormones, genes and proteins such as corticotrophin factor (CRF), vasopressin (AVP) and glucocorticoid receptor (GR) (10). Studies have shown that the methamphetamine users exhibit high levels of ACTH and lower cortisol levels compared to the control group after 96 hours of abstinence (5). On the other hand, HPA axis hyperactivity is associated with symptoms of depression (11).

Syndrome of depression is common among users, especially in early methamphetamine abstinence and is often associated with a craving that can aggravate the relapse (12). Furthermore metabolic functioning in the anterior belt is related to the symptoms of depression in methamphetamine users (13). Symptoms of depression are more likely among female than male users, (14) because glucocorticoid secretion in women is biologically higher than men; and its increased levels can lead to the changes in gene and proteins (CRF, AVP, GR). It can also cause increased secretion of stress hormones and the return of the anxiety and depression symptoms which often can be seen during abstinence.

The relationship between high levels of glucocorticoids in female users and mental and behavioral consequences of this process are currently unknown. However, several factors can cause the psychological emergence of depression symptoms in female users of Met including lack of desirable body image, low self-esteem, lack of social support and eating disorders (15). This increase in cortisol levels due to methamphetamine abuse can also affect the growing fetus. In a two-year follow-up study, the stress-induced cortisol levels were significantly higher in babies exposed to methamphetamine (16). These changes were observed in the form of arousal in these babies (17, 18) and increased emotional responses, depression symptoms, and anxiety in 3-5 years old children (19, 20).

Surgery, anesthesia, trauma, and severe illnesses result in elevated plasma ACTH and cortisol levels. A hernia is a gap or space in the strong tissue that holds muscles in place. A hernia occurs when the inside layers of the abdominal muscle are weakened, resulting in a bulge or tear. Inguinal hernia surgery refers to a surgical operation for the correction of an inguinal hernia. Surgery is not suggested in most cases, and if the hernia produces no symptoms, watchful waiting is the recommended option. This surgery is stressful for patients.

A literature review has shown the contradictory reports of changes in response to stress in Met users. Some studies have rejected the effect of psychological stress on cortisol secretion in chronic methamphetamine and cocaine dependent subjects (21), while some studies have reported reduction in cortisol levels following the social stress on those using ecstasy (22) and cocaine or increased levels of cortisol in cocaine users in response to the stressful images (23). Given the contradictory findings in the field and regarding the fact that treatment of methamphetamine-dependent individuals is very difficult in particular through psychotherapy interventions (24), it is necessary to investigate the biological basis and the relationship between these failures with the cognitive component accompanied by methamphetamine abuse. Therefore, the present study investigates the relationship between plasma levels of cortisol with depression, stress and anxiety indices in chronic methamphetamine-dependent patients and normal individuals undergoing inguinal hernia surgery.

Methods

Data

The present study is a descriptive correlational research. The related data were collected since March 15 to June 9, 2015 based on the purposeful selection. Two physicians, a psychiatrist, and a nurse participated, after selecting the participants and dividing them into two groups of active users and non-user. The inclusion and exclusion criteria were controlled precisely.

The methamphetamine-dependent group had at least a 3-year history of methamphetamine abuse. Inclusion criteria were the ability to read and to write, addiction history of 2 to10 years and using 0.5-1 grams per day. Furthermore, the exclusion criteria included simultaneous dependence on other drugs, a history of certain diseases or severe mental disorders and the use of neuroleptic drugs and drug allergy. The Structured Clinical Interview for DSM Disorders (SCID) was performed during the screening phase to determine the clinical diagnosis of substance abuse. The baseline demographic questionnaire was completed by participants (response rate= 0.93).

To compare two groups of dependent and non-dependent, Plasma cortisol levels were collected in three stages immediately after induction of anesthesia, twelve and twenty-four hours after surgery through a peripheral vein. Then, it was centrifuged for twelve minutes with the speed of three thousand cycles per minute (response rate=0.87). Before surgery, all patients completed a self-report questionnaire of Depression Anxiety Stress Scale 21 (DASS-21) to assess the behavioral indicators (response rate=0.94). Finally, the results were analyzed using t-test and Pearson's correlation coefficients.

The total sample size for participating in this study based on the related literature included 70 people. Based on non-random targeted sampling, during 4 months, with the help of two physicians and a psychiatrist, a list of the future references for the inguinal hernia surgery was provided. Then, the arrangements for referring them to a psychologist; the inclusion criteria and the willingness to participate in the study was checked based on the data related to the admission interview and their dependence on methamphetamine. After acquiring the required criteria to be included in the study, the patients were interviewed and then 35 male methamphetamine-dependent patients were included in the study after obtaining their consent. To control the intervening variables, 35 patients were selected for inguinal hernia surgery from among those who had no record of drug abuse. Then they were homogenized based on the demographic characteristics of age, marital status, educational level and job with the methamphetamine-dependent patients.

Ethical Principles

In this study, the informed consent was obtained without coercion, threat, enticement and seduction. Further the participants' decisions to refuse or accept to participate in the study were respected. All stages of designing, conducting and reporting were based on human dignity; respect and protection of the participants' physical and mental integrity so that conducting the research would not cause a delay in the process of medical care for the participants.

Research Instruments

Data collection was done based on using

the available data, observations, interviewing the participants and using questionnaires. In this study four instruments were used including the researcher made demographic questionnaire, the Structured Clinical Interview for DSM-IV Disorders (SCID) used during the screening phase for the clinical diagnosis of drug abuse, the Depression Anxiety Stress Scale 21 (DASS-21) and Radioimmunoassay (RIA) to measure cortisol level.

1) Demographic Questionnaire was developed and applied by the researcher to collect the personal information such as age, education, socioeconomic condition, disease background, treatment background and the duration of drug use.

2) The Structured Clinical Interview for Disorders DSM- IV (SCID) is a clinical interview that is applied for diagnosis of the disorders on axis one based on DSM-IV. The inter-rater reliability coefficient was reported as 0.60 (25). Diagnostic agreement of this tool in Persian for most specific and general diagnoses with the reliability higher than 0.60, was satisfactory. Kappa coefficient for all current and lifetime diagnoses was obtained 0.52 and 0.55, respectively (26).

3) Depression, Anxiety & Stress Scale (DASS-21) is designed by Lovibond. It is a set of three self-report subscales for measuring negative emotional states of depression, anxiety and stress. Sahebi, Asghari and Salari (27) reported the correlation of 0.70 between DASS Depression Subscale and Beck's Depression Questionnaire, correlation of 0.67 between DASS Anxiety Subscale and Zung's Anxiety Questionnaire and correlation of 0.49 between DASS Stress Subscale and Perceived Stress Test in Iran.

4) Radioimmunoassay (RIA) is an instrument which is widely used in medical laboratories to verify hormones, drugs, and other organic species worldwide. Radioactive iodine is used in this method to create a signal.

Statistical analysis

Due to the type of the present study and previous research, the parametric t-test was used in the present study to measure the cortisol levels in plasma in two groups of methamphetamine-dependent and non-dependent participants. In previous studies, the differences in cortisol levels in methamphetamine-dependent and non-dependent participants were taken into account. The present researcher examined this difference using a t-test ($p<0.05$).

The difference between the behavioral indicators in methamphetamine-dependent and non-dependent patients played a significant role in understanding and explaining the importance of psychological factors affecting the trend toward stimulus. Thus, the mean of the above-mentioned indices in both groups was analyzed by t-test. Since the literature review indicated the importance of the relationship between cortisol levels and behavioral indices, therefore, considering the interval scale of the relationship between cortisol level and behavioral indices, the relationship was evaluated using Pearson's correlation coefficient ($p=0.01$). It is hypothesized that the change in cortisol level due to chronic dependence on methamphetamine explains the behavioral changes which lead to failure process and returning to drug abuse through creating a vicious cycle.

Results

Table 1 shows the research instrument, purpose, and timing of evaluations. To easily understand the research process, four instruments were used in this study, the timing and purpose of which are shown in Table 1. The Structured Clinical Interview for DSM-IV Disorders (SCID) was used during the screening phase for clinical diagnosis of drug abuse. The researcher-made demographic questionnaire was used before the experiment to define the demographic features of the participants including marital status, job, education, and age. To measure cortisol level in plasma, Radioimmunoassay (RIA) was used in three time

Table 1. the research instrument, purpose, and timing

Instruments	Purpose	Timing
SCID	Clinical diagnosis of drug abuse	During the screening phase
Demographic questionnaire	Evaluation of demographic features	Baseline
Radioimmunoassay (RIA)	Cortisol measurements	Hours 0, 12 and 24
self-report questionnaires of Depression Anxiety Stress Scale 21 (DASS-21)	Diagnosis of depression, anxiety and stress	Three days after the cortisol measurements

Table 2. Demographic features of the participants

Indices	Group	Methamphetamine- dependent		Non-dependent	
		N	%	N	%
Martial statues	Single	14	40	11	31/4
	Married	21	60	24	68/6
Education	Lower than high school degree	9	25/7	11	31/4
	Higher than high school degree	26	74/3	24	68/6
Age	Under 25	8	22/9	9	25/7
	25 and over	27	77/1	26	74/3
Occupation	Employed	25	71/4	23	65/7
	Unemployed	10	28/6	12	34/3

series of 0 (upon induction of anesthesia), 12 and 24 hours after the surgery. Finally, the self-report Depression Anxiety Stress Scale 21 (DASS-21) was used three days after surgery to evaluate the behavioral indices of depression, anxiety and stress and due to the existed limitations in recovering process.

Demographic features of the Participants

Table 2 shows the frequency distribution of the research participants based on their demographic features including marital status, education, age, and occupation. As it is seen, the number of those who were married and had a higher than high school degree is more than those who are single and had a lower than high school degree. On the other hand, most of the research participants were over 25 years old; most of whom were employed. From among 70 participants of the study which are equally divided into two groups, 21 in the dependent group (60%) were married and 14 (40%) were single. This frequency ratio is slightly higher than married participants in non-dependent group (68.6%). Regarding educational degree, 26 out of 35 methamphetamine-dependent participants (74.3%) had an educational degree of higher than high school. Regarding this item, 24 participants (68.6%) were in the non-dependent group. In terms of age, most of the participants in both groups were over 25 years old including 77.1% and 74.28% in dependent and non-dependent groups, respectively. 71.4% of the participants in the dependent group and 65.7% in the non-dependent group were employed.

Comparison of Cortisol Levels in Plasma

Based on the data analysis, there was no significant difference between the levels of cortisol during zero hour (pure consciousness) (dependent group: 194±79 versus Non-dependent group: 221±10) and 12 hours after surgery (dependent group: 143±54 versus Non-dependent group: 169±47); but 24 hours after surgery, there was a significant difference between methamphetamine-dependent and non-dependent group in terms of cortisol level in plasma (dependent group: 173±48 versus Non-dependent group: 89±37, $p<0.05$).

As it is seen in Figure 1, the amount of cortisol level in plasma is shown in three periods of time. Accordingly, there was no significant difference between the levels of cortisol during zero hour (pure consciousness) and 12 hours after surgery; but 24 hours after surgery, there was a significant difference between methamphetamine-dependent and non-dependent groups regarding cortisol level in plasma ($p=0.05$). The amount of cortisol level in plasma is shown in three periods of time in Figure 1. Table 3 shows the mean (SD) of depression, anxiety and stress index.

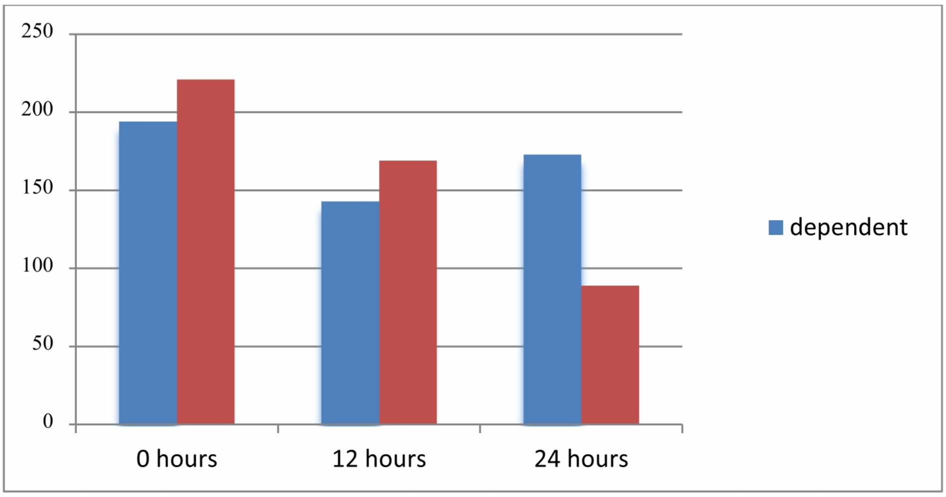

Fig. 1. the methamphetamine-dependent and non-dependent groups' difference regarding Cortisol level in three periods of time

Table 3. Descriptive statistics of the depression, anxiety and stress variables

Group	Index	Mean	SD
Dependent	Depression	44.1*	2.12
	Anxiety	33.0	2.37
	Stress	35.8	1.93
Non-dependent	Depression	29.1	2.03
	Anxiety	32.7	1.97
	Stress	36.3	3.11

*p<0.05

Comparing depression, anxiety and stress indices

According to the data shown in Table 3, the index of depression in the methamphetamine-dependent group was significantly different from those in the non-dependent group ($p<0.05$). Two groups were not significantly different regarding anxiety index. The same condition was observed for stress index. The results of the correlation coefficient are shown depression index of the methamphetamine-dependent group was significantly different from those in the non-dependent group ($p<0.05$). Furthermore, Pearson analysis was indicated, there was no significant difference between depression index and cortisol level ($p=0.001$, $r=0.14$).

Discussion

Methamphetamine abuse has become a growing phenomenon and one of the main problems in health systems all around the world. What makes understanding the nature of the challenge and consequently efficient planning therapeutic interventions a challenge is the industrial nature of methamphetamine which is, in turn, the results in different psychological and neurological different consequences compared to the traditional drugs abuse. The available therapeutic interventions could not significantly affect the healing process in the users due to the complex nature of the methamphetamine. So that, the relapse rate was significant in the users, and 61% of them relapsed within a year after participating in treatment programs, and only 13% of methamphetamine users avoid using it again during the 5 years after treatment (28). From a clinical point of a wide range of psychological damage can be observed in methamphetamine users (29). Biological basis of methamphetamine dependence is also a key component in explaining the nature of pathogenicity in these patients. Research suggests that chronic methamphetamine users show changes in the HPA axis (11,12). Increased corticotrophin can increase cortisol levels, and corticotropic secretion causes symptoms of depression and anxiety both of which are associated with relapse (30). Long-term stress and damage in the hippocampus and frontal cortex function can also lead to distortion in the performance of HPA axis and behavioral problems which are seen in patients with drug dependence (9). This study showed that cortisol levels in chronic methamphetamine-dependent patients in response to alarming events such as inguinal surgery was significantly higher than non-dependent patients. This finding is consistent with previous findings. Changes in cortisol levels are intensified due to a confrontation with the phenomenon of pain and anxiety (31).

In the study of Gera and colleagues (22) cortisol levels in methamphetamine users were reported to be higher than the control group. There are also similar findings in animal samples. For example, monkeys exposed to methamphetamine showed considerable levels of cortisol over 24 hours (32). The literature review indicates an abnormality in behavioral moods specifically creating episodes of depression in chronic methamphetamine-dependent users. In the study of Sample and colleagues, (33) the symptoms of depression in young women consuming methamphetamine were significantly higher than women in the control group. Injecting high doses of methamphetamine can cause depression-like behavior in mice (34). In the same study, exposure to methamphetamine caused increased depressive behavior in adult mice (35). The chronic methamphetamine-dependent patients in surgery had unpredictable the drop in blood pressure due to the abnormal catecholamine receptors (36). The present study aimed to examine the relationship between plasma levels of cortisol with depression, stress and anxiety indices in chronic methamphetamine-dependent patients and normal individuals undergoing inguinal hernia surgery. The results showed that cortisol level in methamphetamine-dependent patients was significantly higher than the non-dependent group. The rate of depression in chronic methamphetamine-dependent patients was significantly more than the non-addicted group. However, there was no significant relationship between the two components of cortisol levels and depression. The above findings showed the importance of the biological and psychological bases of addiction to a stimulant drug which should be considered in defining a comprehensive treatment method.

Conclusion

The present study was an attempt to find the assumed relationship between methamphetamine users and cortisol level and if the increase in cortisol level would result in any changes in mood index. The present study found that cortisol level in acute methamphetamine-dependent addicts was significantly higher than non-users in the face of some stressors such as inguinal hernia surgery (at 24 hours after experiencing the stressor). As the review of the literature showed, changes in cortisol level are intensified due to facing the sudden pain of anxiety. On the other hand, from among three examined mood indices (including depression, anxiety and stress) only depression index showed a significance difference compared to the normal group ($p<0.05$). Another aspect of the present study was to examine the probable relationship between cortisol level and depression index, a component which plays an important role in biological etiology of the behavioral disorders among the methamphetamines users. Findings indicated that there was no significant relationship between the cortisol level and depression index ($p=0.001$). In general, the hypothalamus-pituitary-adrenal axis which is the trigger for the secretion of cortisol can be considered as the key and yet vulnerable structure in the stress response in methamphetamine users. However, there is a need for more investigations about the relationship between this structure and depression index. Finally, the controlled examination with random sampling, longer time and using newly emerging measurement methods is recommended so that by more comprehensive and wider examinations the following questions can be answered: Is there any linear relationship between the drug consumption level and cortisol level? What biological or psychological indices can modify the cortisol response to the stressors? What are the intermediary variables in the relationship between methamphetamine use and depression period?

Limitations

This study has particular limitations. The first limitation of this study is a small sample size. Although the number of participants did not decrease in this study, small sample size is one of the limitations that obstacles accurate measurement of the effect. The second limitation is the self-report tools. These tools have some essential problems (measurement error, lack of self insight etc.) The third limitation is related to lack of contextual and in dividable factors control. It is possible that participants overestimated the effect of the program because of some contextual factors. It is also recommended to use samples with a larger size to obtain a true effect size.

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Conflict of Interests

The Authors have no conflict of interest.

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