Original Article

DOI: 10.7860/JCDR/2021/48387.14787

Pharmacology Section

A Prospective Observational Study on the Effects of Antidepressant Treatment on Hypothalamic-Pituitary-Adrenal Axis Regulation in Treatment Resistant Depression

KAVITA[1], MANOJ KUMAR SAHU[2], PRAVIN GUNDERAO DHONE[3], RAVI KANT TIWARI[4], RAJESH HISHIKAR[5]

ABSTRACT

Introduction: Dysregulation of Hypothalamic-Pituitary-Adrenal (HPA) axis can reduce the effects of antidepressants. Salivary cortisol level and Hamilton Depression Rating (HAM-D) score can be used to assess the level of improvement in the HPA axis and depressive disorders.

Aim: To evaluate the changes in salivary cortisol level and HAM-D score in patients of Treatment Resistant Depression (TRD) and to investigate the association between them.

Materials and Methods: The present prospective cohort study was conducted in the Department of Pharmacology and Psychiatry at Pt. JNM Medical College and Dr. BRAM Hospital Raipur (CG) over a period of one year, from June 2014 to June 2015. The participants were 52 diagnosed cases of TRD according to Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria, who were taking antidepressant medications for at least four weeks. The salivary cortisol values and HAM-D scoring were done at baseline and follow-up at eight weeks and 16 weeks and compared by student's t-test and one-way ANOVA.

Results: A significant difference ($p<0.001$) was noted in the mean salivary cortisol levels (1.15±0.31 and 0.72±0.24) and mean HAM-D (29.67±1.43 and 16.26±7.08) scores at baseline and subsequent follow-up, respectively.

Conclusion: The therapeutic benefit of antidepressants could be due to alteration of HPA axis functioning.

Keywords: Hamilton depression rating, Neurotransmission, Salivary cortisol

INTRODUCTION

Depression is a common mood disorder characterised by feeling depressed mood most of the day, loss of interest in most regular activities, fatigue or low energy, feeling of guilt or worthlessness, loss of concentration or indecisiveness, disturbed sleep, change in appetite, psychomotor retardation, loss of libido and recurring thoughts of death or suicide [1]. The important risk factors are genetic predisposition, female gender and victims of trauma and abuse [2]. Clinical guidelines recommend the use of antidepressant medication for the treatment of a moderate to severe depressive episode [3].

The majority of antidepressants, on long-term administration, increase the forebrain levels of 5-hydroxytryptamine (serotonin, 5-HT). It has been observed that acute depletion of tryptophan (the precursor of 5-HT) can lead to the rapid recurrence of depressive mood in patients treated with antidepressants and the underlying mechanism involves alteration of hypothalamic-pituitary-adrenal (HPA) axis [4]. It is an established fact from animal and human studies that glucocorticoids influence serotonergic neurotransmission. They can alter the sensitivity of 5-HT autoreceptors and efficacy of postsynaptic 5-HT receptors [5-7].

Hyperactive HPA axis is a consistent finding in depression and altered HPA axis can reduce the effects of antidepressants [8]. The recent reviews confirm the association between HPA axis activity, cortisol and depression and it has been observed that the morning and evening cortisol concentration is increased in patients with depression and their morning-to-evening slope is flatter than of healthy controls [9].

Cortisol (also called as stress hormone) can be used as marker of HPA axis activity and can be measured in blood, urine and saliva. Over the past two decades, saliva sample to measure the cortisol level has gained increasing acceptance and is the method of choice in research studies. The saliva cortisol is the free fraction and it is more closely correlated with the free cortisol fraction in the serum compared to total serum cortisol [10]. Although cortisol has been extensively measured in depression even in patients experiencing multiple depressive episodes, the effect of cortisol has never been clearly evaluated in Treatment Resistant Depression (TRD). The HAM-D/HDRS (Hamilton Depression Rating) scale is the most widely used clinician-administered depression assessment scale designed to rate the severity of depression in patients [11]. Keeping the above facts in mind, this study was aimed to evaluate the changes in salivary cortisol level and HAM-D score in patients of treatment resistant depression and to investigate the association between them.

MATERIALS AND METHODS

The present prospective cohort study was conducted in the Department of Pharmacology and Psychiatry at Pt. JNM Medical College and Dr. BRAM Hospital Raipur (CG) over a period of one year, from June 2014 to June 2015. The study was commenced after clearance from Institutional Ethical committee.

The study included the patients attending the psychiatry OPD with diagnosis of TRD [12]. Depression may be considered resistant to treatment when at least two trials with antidepressants from different pharmacologic classes (adequate in dose, duration, and compliance) fail to produce a significant clinical improvement [13]. Adequate dose is defined as the standard recommended dose of the antidepressant while adequate duration of treatment is defined as at least four consecutive weeks of treatment, during which the patient has had an adequate dose for at least three weeks.

Sample size calculation: Sample size for this study was calculated by using the formula $\{n=z^2.pq/d^2\}$, where q=1-p. By applying the values of z, d (absolute precision) and p (expected proportion in the population, which was found from previous studies) to the above

formula as 1.96, 5% and 4%, respectively, the calculated sample size was found to be 59 [14].

Inclusion criteria: A total of 70 subjects of TRD aged 18 years or above, who had used antidepressants for four consecutive weeks, were recruited after obtaining written informed consent.

Exclusion criteria: The exclusion criteria for the participants were patients having hormonal disorders, other psychiatric illnesses, pregnant and lactating mothers, or the patients having substance abuse disorders.

The levels of the salivary cortisol (measured by the salimetric salivary cortisol ELISA kit), and mean HAM-D Score were taken as baseline and then the two follow-up at the interval of eight weeks. Hamilton Rating Scale for Depression (HAM-D, the 21-Item scale; 1960) was applied to the subjects by a trained psychiatrist to assess severity of depression [15]. Subjects included had a cut-off score ≥17. The treatment option in such patients could be substitution with different group of antidepressants, combination of antidepressants or combination of non-antidepressants such as an atypical antipsychotic or benzodiazepine [16,17]. At the follow-up, subjects were classified as responders or non-responders based on a 50% reduction of the HAM-D 21 Item Rating Scale at discharge point (Keller, 2003) [18]. The range of basal salivary cortisol between 0.112 to1.551 µg/dL in the morning sample was taken as reference value [19]. Of the total recruited subjects only 52 subjects came to regular follow-up at eight and 16 weeks.

STATISTICAL ANALYSIS

The salivary cortisol levels and mean HAM-D scores were noted at baseline and follow-up and these values were compared by student's t-test, one-way ANOVA test and correlated with Pearson's rank order correlation. Statistical significance was set at $p<0.05$. The SPSS 16.0 software was used for data analysis (Statistical Package for the Social Sciences version 16.0; SPSS, IBM Corporation, Chicago, Illinois, USA).

RESULTS

The demographic data showed that out of 52 subjects included in this study, 24 (46.15%) were males and 28 (53.84%) were females. The mean age in study group was found to be 41.2±10.3 years. As shown in [Table/Fig-1], majority of the subjects (42.3%) were housewives. Family history of depression was present in 5 (9.61%) subjects, while family history of other psychiatric illness was present in 2 (3.84%) subjects. Mean duration of illness was found to be 16.4±12.4 months and mean duration of treatment was 9.8±7.9 months.

Characteristics		No. of subjects	Percentage
Occupation	Agriculture	10	19.2
	Self-employed	9	17.3
	Service	11	21.1
	Housewife	22	42.3

[Table/Fig-1]: Occupation wise distribution of study subjects.

The mean HAM-D score in the study subjects at baseline was found to be 29.67±1.43 which subsequently changed to 17.46±6.29 and 16.26±7.08 at the first and second follow-up, respectively. Statistically significant difference ($p<0.01$) was found on comparing the mean HAM-D scores at baseline vs first follow-up and at baseline vs second follow-up, while it was insignificant between first and second follow-up [Table/Fig-2].

The baseline mean salivary cortisol level (µg/dL) in the study subjects was found to be 1.15±0.31 which was subsequently changed to 0.79±0.22 and 0.72±0.24 at the first and second follow-up, respectively. Statistically significant difference ($p<0.001$) was noted on comparing the mean salivary cortisol level at the baseline and two follow-up by one way ANOVA test, but the difference was insignificant between first and second follow-up [Table/Fig-2].

Characteristics	Baseline	After 8 weeks (1st follow-up)	After 16 weeks (2nd follow-up)	p-value (Student t-test)
Outcome HAM-D score Mean±SD	29.67±1.43	17.46±6.29	16.26±7.08	<0.01: Baseline and 8 weeks
				<0.01: Baseline and 16 weeks
				>0.05: 8 weeks and 16 weeks
				<0.001 by one-way ANOVA.
Salivary cortisol levels (µg/dL) Mean±SD	1.15±0.31	0.79±0.22	0.72±0.24	<0.01: Baseline and 8 weeks
				<0.01: Baseline and 16 weeks
				>0.05: 8 weeks and 16 weeks
				<0.001 by one-way ANOVA.

[Table/Fig-2]: Mean HAM-D score and mean salivary cortisol levels at baseline and follow-up.
p-value <0.001 was considered statistically significant

Out of the 52 subjects, 40 of them responded to treatment with decrease in both the HAM-D score and salivary cortisol value. Nine of them showed slight decrease in HAM-D scoring and no change in salivary cortisol levels. Three of them showed slight change in salivary cortisol values but the HAM-D score did not improve.

Mean change in salivary cortisol level was found to be significantly higher (0.53±0.31) compared to non-responders (-1.72±1.95) when the difference was assessed using student's t-test ($p<0.0001$) [Table/Fig-3].

Characteristic	Responders n=40	Non-responders n=12	p-value
Change in salivary cortisol levels (µg/dL) Mean±SD	0.53±0.31	-1.72±1.95	<0.0001 by student's t-test

[Table/Fig-3]: Comparison between change in salivary cortisol levels in responders and non-responders depression subjects.
p-value <0.001 was considered statistically significant

Change in HAM-D score over the period of follow-up and change in salivary cortisol level were correlated with Pearson's rank order correlation, which indicated moderately strong positive correlation [Table/Fig-4].

	Mean	Variance	SE	Pearson's r	r^2	p-value
Change in HAM-D score	13.4±7.5	57.2	1.0	0.614	0.377	<0.0001
Change in salivary cortisol levels (µg/dL)	0.4±0.3	0.12	0.04			

[Table/Fig-4]: Pearson's correlation between changes in HAM-D score and changes in salivary cortisol levels.
p-value <0.001 was considered statistically significant

DISCUSSION

The aim of this study was to evaluate the changes in salivary cortisol level and HAM-D score in patients of major depressive disorders, who were considered resistant to treatment. Out of the 52 subjects included in this study, the majority (53.8%) were females and housewives (42.3%). In this study, the mean HAM-D score of the study subjects was reduced from baseline to subsequent follow-up and there was a significant statistical difference ($p<0.001$) when these were compared by one-way ANOVA test. The baseline mean salivary cortisol level was above the reference range of normal (0.112-1.551 µg/dL) in the study subjects which subsequently reduced on antidepressant therapy as noted by the two follow-up at eight weeks interval, and the difference was statistically significant ($p<0.001$).

Earlier studies have shown that the salivary cortisol levels increase 50-75% within the first 30 minutes after awakening and this morning surge of cortisol is termed as Cortisol Awakening Response (CAR) and is considered to be a key determinant for HPA axis evaluation [20,21,22]. The findings of the present study were similar to other studies where the use of antidepressants has been found to lower waking cortisol level [23,24]. Since, hyperactivity of the HPA axis as shown by waking cortisol level in the patients of depression is a common finding, the therapeutic benefit of antidepressants could be related to the direction of the effects of antidepressants on waking cortisol levels [25].

Though the hyperactivity of HPA axis had been shown in many studies in patients of depression, there are few exceptions too. A normal or low HPA activity has been observed in chronic depressive patients than non-chronic patients and the patients with multiple depressive episodes have lower HPA axis activity than patients with fewer depressive episodes [26]. Some studies reported lower or unchanged basal levels and variously altered (decreased, increased and unchanged) cortisol suppression in the users of Selective Serotonin Reuptake Inhibitors (SSRIs) group of antidepressants [27,28]. There are several possible explanations for these discrepancies. Associations of reduced cortisol levels with a positive treatment response indicated that normalised cortisol levels may not reflect antidepressant use alone. A biological explanation for this atypical pattern could be due to the effects of antidepressants on the two corticosteroid receptors, Glucocorticoid Receptor (GR) and Mineralocorticoid Receptor (MR). A few animal studies found that chronic administration of antidepressants resulted in upregulation of these receptors which may contribute to the flattened CAR [29]. In the studies conducted by Eiring A and Sulser F and Johansson IM et al., the authors found increased suppression of cortisol level due to overexpression of GR [30,31]. In the Netherlands Study on Depression and Anxiety (NESDA), elevated cortisol levels were found in both current and remitted depressed subjects, the altered HPA axis activity was found to be independent of treatment success [32,33]. Therefore, additional randomised interventional studies are needed to investigate the association between the different cortisol indicators and the treatment response (assessed by HAM-D score).

Limitation(s)

The major limitation of this study was that the study did not investigate the association between different subtypes of antidepressants such as SSRIs Tricyclic Antidepressants (TCAs) and other antidepressants on some more cortisol parameters such as evening cortisol secretion and the slope of morning to evening cortisol secretion.

CONCLUSION(S)

There were changes in salivary cortisol level and HAM-D score from baseline to subsequent follow-up and these changes were correlated with Pearson's rank order correlation which indicated moderately strong positive correlation between change in serum cortisol and change in HAM-D score. The use of antidepressants could alter the functioning of HPA axis. Further research by conducting randomised interventional studies including different groups of antidepressants on different cortisol indicators can help in the better understanding of the therapeutic effects of antidepressants and their association with HPA axis in the patients of major depressive disorders and TRD.

REFERENCES

[1] Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, et al. Major depressive disorder. Nature Reviews Disease Primers. 2016;2:16065.

[2] Bale TL, Epperson CN. Sex differences and stress across the lifespan. Nat Neurosci. 2015;18(10):1413-20.

[3] Knorr U, Vinberg M, Gether U, Winkel P, Gluud C, Wetterslev J, et al. The effect of escitalopram versus placebo on perceived stress and salivary cortisol in healthy first-degree relatives of patients with depression- A randomised trial. Psychiatry Res. 2012;200:354-60.

[4] Mikkelsen JD, Hay-Schmidt A, Kiss A. Serotonergic stimulation of the rat hypothalamo-pituitary-adrenal axis: Interaction between 5-HT1A and 5-HT2A receptors. Ann N Y Acad Sci. 2004;1018:65-70.

[5] Bjartmar L, Johansson IM, Marcusson J, Ross SB, Seckl JR, Olsson T. Selective effects on NGFI-A, MR, GR and NGFI-B hippocampal mRNA expression after chronic treatment with different subclasses of antidepressants in the rat. Psychopharmacology. 2000;151:07-12.

[6] McAllister-Williams RH, Massey AE, Fairchild G. Repeated cortisol administration attenuates the EEG response to buspirone in healthy volunteers: Evidence for desensitization of the 5-HT1A autoreceptor. J Psychopharmacol. 2007;21:826-32.

[7] Brouwer JP, Appelhof BC, Van Rossum EF, Koper JW, Fliers E, Huyser J, et al. Prediction of treatment response by HPA-axis and glucocorticoid receptor polymorphisms in major depression. Psychoneuroendocrinology. 2006;31(10):1154-63.

[8] Carpenter T, Grecian S, Reynolds R. Sex differences in early life programming of the hypothalamic-pituitary-adrenal axis in humans suggest increased vulnerability in females. Psychoneuroendocrinology. 2015;61:32.

[9] Dienes KA, Hazel NA, Hammen CL. Cortisol secretion in depressed and at-risk adults. Psychoneuroendocrinology. 2013;38:927-40.

[10] Hinkelmann K, Moritz S, Botzenhardt J, Muhtz C, Wiedemann K, Kellner M, et al. Changes in cortisol secretion during antidepressive treatment and cognitive improvement in patients with major depression: A longitudinal study. Psychoneuroendocrinology. 2012;37:685-92.

[11] Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: Fourth Generation of Progress. New York, NY: Raven Press; 1995:1081-97.

[12] Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am. 1996;19:179-200.

[13] Malhi GS, Parker GB, Crawford J, Wilhelm K, Mitchell PB. Treatment-resistant depression: Resistant to definition? Acta Psychiatr Scand. 2005;12:302-09.

[14] Janicak PG, Dowd SM. Treatment-resistant depression: An update on diagnosis and management. Psychopharm Review. 2009;44:41-48.

[15] Dunner MD. Prospective long term multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry. 2006;67(5):688-95.

[16] Chanaka W, Sachdev P. Treatment-resistant depression: Critique of current approaches. The Australian and New Zealand Journal of Psychiatry. 2008;42(9):751-62.

[17] Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. J Clin Psychiatry. 2006;67(suppl 6):16-22.

[18] Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: Remission and beyond. JAMA. 2003;289:3152-60.

[19] McKay MS, Zakzanis KK. The impact of treatment on HPA axis activity in unipolar major depression. Journal of Psychiatric Research. 2010;44(3):183-92.

[20] Bhagwagar Z, Hafizi S, Cowen PJ. Increased salivary cortisol after waking in depression. Psychopharmacology. 2005;182:54-57.

[21] Dedovic K, Ngiam JN. The cortisol awakening response and major depression: Examining the evidence. Neuropsychiatr Dis Treat. 2015;11:1181-89.

[22] Ehnvall A, Sjogren M, Zachrisson OC, Agren H. HPA axis activation determined by the CRH challenge test in patients with few versus multiple episodes of treatment refractory depression. Eur Arch Psychiatry Clin Neurosci. 2004;254(6):349-55.

[23] Stimpson N, Agrawal N, Lewis G. Randomised controlled trials investigating pharmacological and psychological interventions for treatment refractory depression. Systematic review. Br J Psychiatry. 2002;181:284-94.

[24] Fischer S, Macare C, Cleare AJ. Hypothalamic-pituitary-adrenal (HPA) axis functioning as predictor of antidepressant response-meta-analysis. Neurosci Biobehav Rev. 2017;83:200-11.

[25] Adam EK, Kumari M. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology. 2009;34:1423-36.

[26] Adam EK, Quinn ME, Tavernier R, McQuillan MT, Dahlke KA, Gilbert KE. Diurnal cortisol slopes and mental and physical health outcomes: A systematic review and meta-analysis. Psychoneuroendocrinology. 2017;83:25-41.

[27] Juruena MF, Cleare AJ, Papadopoulos AS, Poon L, Lightman S, Pariante CM. The prednisolone suppression test in depression: Dose-response and changes with antidepressant treatment. Psychoneuroendocrinology. 2010;35:1486-91.

[28] Wilhelm I, Born J, Kudielka BM, Schlotz M, Wust S. Is the cortisol awakening rise a response to awakening? Psychoneuroendocrinology. 2007;32(4):358-66.

[29] Pariante CM, Hye A, Williamson R, Makoff A, Lovestone S, Kerwin RW. The antidepressant clomipramine regulates cortisol intracellular concentrations and glucocorticoid receptor expression in fibroblasts and rat primary neurones. Neuropsychopharmacology. 2003;28:1553-61.

[30] Eiring A, Sulser F. Increased synaptic availability of norepinephrine following desipramine is not essential for increases in GR mRNA-short communication. Journal of Neural Transmission. 1997;104:1255-58.

[31] Johansson IM, Bjartmar L, Marcusson J, Ross SB, Seckl JR, Olsson T. Chronic amitriptyline treatment induces hippocampal NGFI-A, glucocorticoid receptor and mineralocorticoid receptor mRNA expression in rats. Molecular Brain Research. 1998:62:92-95.

[32] Penninx BW, Beekman AT, Smit JH, Zitman FG, Nolen WA, Spinhoven P, et al. NESDA Research Consortium. The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. Int J Methods Psychiatr Res. 2008;17(3):121-40.

[33] Penninx BW, Nolen WA, Lamers F, Zitman FG, Smit JH, Spinhoven P, et al. Two-year course of depressive and anxiety disorders: Results from the Netherlands Study of Depression and Anxiety (NESDA). J Affect Disord. 2011;133(1-2):76-85.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pharmacology, Government Medical College, Ambikapur, Surguja, Chhattisgarh, India.
2. Associate Professor, Department of Psychiatry, Pt. J.N.M. Medical College, Raipur, Chhattisgarh, India.
3. Professor, Department of Pharmacology, Government Medical College, Ambikapur, Surguja, Chhattisgarh, India.
4. Associate Professor, Department of Pharmacology, Government Medical College, Ambikapur, Surguja, Chhattisgarh, India.
5. Professor, Department of Pharmacology, Pt. J.N.M. Medical College, Raipur, Chhattisgarh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ravi Kant Tiwari,
Associate Professor, Department of Pharmacology, Government Medical College, Ambikapur, Surguja, Chhattisgarh, India.
E-mail: drrkt1912@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 06, 2021
- Manual Googling: Mar 08, 2021
- iThenticate Software: Mar 23, 2021 (21%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 05, 2021**
Date of Peer Review: **Feb 04, 2021**
Date of Acceptance: **Mar 10, 2021**
Date of Publishing: **Apr 01, 2021**