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EFFECT OF ZINC SUPPLEMENTATION ON ANTIDEPRESSANT THERAPY AND SERUM ZINC LEVEL IN UNIPOLAR DEPRESSION: A DOUBLE-BLIND RANDOMIZED CONTROLLED STUDY

Clinical Research

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ABSTRACT

Background: Recent studies have shown importance of zinc in pathogenesis of depression. However, literature on efficacy of adjunctive zinc supplementation for unipolar depression is conflicting.

Aims: The aim of our study was to assess effectiveness of adjunctive zinc in depression and to assess difference in serum zinc levels before and after treatment.

Methods: Sixty drug naïve or drug free (for ≥2 weeks) subjects having diagnosis of unipolar depression (including recurrent depressive disorder) were recruited and allocated into two groups by simple random sampling. Both groups were assessed with HAM-D, BDI, BSSI and HAM-A. Subjects and raters were blinded to groups. Serum zinc level was assessed. Twenty milligrams of elemental zinc were given daily along with treatment as usual and the other group received treatment as usual only. Assessments were done at baseline and repeated at 2, 4 & 8 weeks.

Results and conclusion: No significant difference was found between zinc group and treatment as usual group in reducing the severity of depressive symptoms. Our study concluded that adjunctive zinc supplementation along with antidepressants have no adjunctive effect on improvement in the severity of depression.

KEYWORDS

zinc; depression; randomized; double blind

INTRODUCTION

Major depressive disorder (MDD) currently ranks as the fourth leading disease burden worldwide and is expected to become the second global disease burden in 2020.[1] Depression represents a substantial public health burden owing to its high prevalence [2-6] and as associated with premature death and disability [7,8] and with a considerable cost of therapy. [9, 10] It affects 4 to 12 percent of men and 12 to 26 percent of women.[11] While MDD is sometimes viewed as one of the most "treatable" conditions, it tends to be recurrent or chronic. [12] Conventional treatment begins with antidepressant monotherapy, but this approach is often ineffective in achieving an adequate clinical response or remission. Regardless of the standard antidepressant medication used to start treatment, initial antidepressant monotherapy has comparable limitations in their overall efficacy.[12] Despite many years of research, the psychopathology of depression, its neurobiological underpinnings and its clinical efficacy to conventional/newer antidepressants are yet unsatisfactory and remains poorly understood. Hence, there is a need to search for newer and more effective and safer adjunctive/add on therapies for the treatment and prevention strategies of depression. During the last few years, many researches have indicated important role of adjunctive zinc supplementation in the management of depression. Lower zinc concentration has been found in depressed patient than physiological normal control [13-15] and there is inverse correlation between zinc levels and severity of depression. [14,15] Further support of the hypothesis that zinc concentration might be sensitive and specific marker of depression is the fact that lower level of serum zinc may be normalized after successful antidepressant therapy. [13, 16, 17] A recent case control study by Styczeńet al. (2017) [18] also confirm the presence of zinc deficiency in the depressive episode and are consistent with most of previous studies. Hence, our study aimed to examine the effect of adjunctive zinc supplementation on severity of depression and serum zinc level among patients of unipolar depression.

METHOD

Study design and participants

The study was a hospital based double blind randomised controlled trial conducted at Central Institute of Psychiatry, Ranchi. Sample size was consisted of 60 diagnosed drug naïve (or drug free for minimum 2 weeks) cases of single depressive episode (F32.XX) or recurrent depressive disorder (F33.XX) according to International Classification of Disease 10th version (ICD-10) - Diagnostic Criteria for Research (DCR)by World Health Organization (WHO, 1993) [19]; of either sex between 18-60 years with written informed consent. Patients having comorbid psychiatric and medical disorder, history of substance use and dependence, other than nicotine and caffeine and those patients who got ECT and multivitamin supplementation were excluded from study.Data was collected between September 2013 and January 2015. The study was approved by the Ethical Committee of the Central Institute of Psychiatry, Ranchi and was registered in Clinical Trial Registry India (CTRI number: CTRI/2017/01/007751; URL:http://ctri.nic.in.)

Sampling and data collection

Following approval from institutional ethics committee, the sample was drawn from inpatients of our institute. A total of 81 patients fulfilled inclusion and exclusion criteria during the study period. Six among them did not give consent for the study. Two patients had been recommended electroconvulsive therapy immediately following admission and thereby were excluded from the study. Following discussion and review after admission, diagnosis was changed in ten patients. Three patients had to be discharged for significant physical illness. Sixty patients were recruited for the study and were allocated into two groups by simple random sampling technique using computer generated randomization. Written informed consent from the patients was taken after explaining the objectives and procedure of the study in detail. A detailed physical examination was done to rule out any major medical or neurological illness. Detailed socio-demographic and clinical data was collected for every subject. Hamilton rating scale for depression (HAM-D), [20] Beck depression inventory (BDI),[21] Beck scale for suicidal ideation (BSSI) [22] and Hamilton rating scale for anxiety (HAM-A)[23] were applied and serum zinc level was measured at baseline and were repeated at 2nd, 4th and 8th weeks. Blood sample were drawn between 8-9 AM and after centrifugation serum was separated and stored at 2-8°C.Serum zinc concentration was measured by colorimetric method (chemistry analysis and semi-automated method); normal reference range 60-120 µg/dl. For patients selected for zinc supplementation, one tablet of zinc sulphate containing 20mg of elemental zinc was given daily along with treatment as usual (TAU + Zn) and other group received treatment as usual only (TAU only). Subjects and rater were blinded to allocated group.

Statistical analysis

Statistical analysis was done using Statistical Packages for Social Science (SPSS) version 20.0 for Windows (Armonk, NY: IBM Corp). The socio-demographic and clinical variables were analysed using

appropriate statistical tests like chi square/Fisher exact test of categorical variables. Continuous variables were analysed after test of normal distribution like Student's t-test for comparing both the groups. Repeated measure ANOVA was used to assess the effect of zinc over time in both groups and between groups as well as interaction of group and time for various clinical scales.Mann-Whitney's U test was applied if data was not normally distributed. Correlation analysis was done to find out any relationship.

RESULTS

Socio-demographic variables

Both groups were comparable for socio-demographic profile. More patients were male, Hindu, unemployed and belonged to nuclear families of rural areas in both groups. There was no significant difference among the groups regarding marital status, religion, occupation, education, family income and family type (Table 1).

Clinical characteristics

About sixty seven percent (66.6%) subjects of TAU + Zn group and 70% subjects of TAU only group were diagnosed as recurrent depressive disorders (F33) according to ICD-10 DCR and the rests were depressive episode. Regarding family history, 11(36.7%) patients of TAU + Zn group and 12 (40%) patients among TAU only group had significant family history of psychiatric illness. Both groups were comparable in age of onset of illness (p=0.22) and duration of illness (p=0.36). Table 2 shows clinical characteristics of both groups. More patients of TAU only group had low baseline zinc level than TAU + Zn group though no statistically significant difference between groups was found (p=0.24) (Table 2).

Efficacy of zinc supplementation on symptoms severity of depression and serum zinc level

Table 3and4 show main effects of time (baseline, 2, 4 and 8 weeks), group and time*group interaction within and between the two groups on various outcome scales. Repeated measures ANOVA was used to assess the effect of zinc over time in both groups and between groups as well as interaction of group and time for various measures which were administered (HAM-D, BDI, BSSI, HAM-A) and serum zinc level. There was significant decrease in severity of psychopathology over time from baseline to 8 weeks in both groups. However, no significant group*time interaction effect was found for any measure (Table -3). There was no significant change in serum zinc over time from baseline to 8 weeks in both. No significant group*time interaction effect was found for serum zinc level (Table-4).

DISCUSSION

The present study was a randomized double-blind controlled study, conducted at Central Institute of Psychiatry (CIP), Ranchi aimed to assess efficacy of zinc supplementation on antidepressant therapy in unipolar depression and serum zinc level. The TAU group in our study did not receive placebo treatment. While this might appear as a limitation, we argue against using placebo in our study. TAU group in our study had received treatment as usual based on existing best-available-therapy. We claim that the use of best available therapy is appropriate when a standard of therapy already exists for depression. Similar evidence has been put forward in literature.[24,25]

4.1. Efficacy of zinc supplementation on antidepressant therapy in unipolar depression:

Our study found significant reduction in severity of depression, suicidal ideation and anxiety over the period from baseline to 8 weeks in both groups. But no significant group*time interaction effect was found for any of them. Thus, our study did not suggest any adjunctive effect of zinc supplementation in improvement of severity of depression.

Role of zinc as antidepressant and its synergistic effects with antidepressants has been demonstrated in some animal studies [26, 27] which had shown zinc had antidepressant effects and enhanced the same of antidepressant medications. Earlier studies in human also have examined the efficacy of zinc supplementation as an adjunct to antidepressant drug therapy (imipramine) as a treatment for depressive symptoms.[15,28,29] After 12 weeks of follow-up, both studies reported a statistically significant difference in all outcome measures of depressive symptoms between placebo and zinc group. Study subjects receiving antidepressant and zinc supplementation recorded a higher difference in baseline and post-intervention depressive symptom scores compared with those receiving antidepressant alone and placebo. However, small sample size limits this finding.[15] Efficacy of zinc supplementation was also examined in their studies in prevention of depressive symptoms amongst the clinically non-depressed general female population.[30,31,32] In addition to depressive symptoms, Sawada and Yokoi (2010) [32] also examined the effect of zinc supplementation on other mood states such as anger, anxiety, and tension. This study showed improvement in all mood states with zinc supplementation. Zinc supplementation also marginally decreased somatic symptoms however the results are less significant (p= 0.069). Our study findings are consistent with an earlier study.[30,31] They examined micronutrient supplementation for the prevention of depressive symptoms. No significant reduction in depressive symptom was found with zinc supplementation. Although this trial has a relatively large sample size (n=369), and when compared to the other studies, has a lower risk of bias related to study design and implementation; zinc supplementation was not the primary intervention of the study but instead was given as a component of micronutrient supplementation where folate was the main intervention. There is a possibility that the net efficacy of zinc supplements is reduced because of nutrient interaction. Similar interaction was suggested in the United States' Women's Health Study in which participants who used multivitamin and mineral supplements in addition to the nutrient of interest, recorded positive outcomes of a lesser magnitude compared to those who did not use supplements. [33] Hence, findings of this study should be interpreted with caution. Given that supplements such as iron are known to inhibit the absorption of zinc, this is a real possibility. [34] In a study conducted by Ranjbar et al. (2013), [35] as an outcome Beck scores was significantly lower (p<0.05) in zinc group compared with the group receiving the placebo. Even after adjusting for the effect of dietary confounding factors, including intake of total fat, saturated fatty acids, monounsaturated and polyunsaturated fatty acids and magnesium, these differences remained significant. As shown in the results, the effects of dietary factors on depression during the study were similar between the two groups. The study by Maserejian et al. (2012) [36] suggest that among women, dietary, supplemental and total zinc were significantly associated with the presence of depressive symptoms. Women in the lowest dietary intake were more likely to have depressive symptoms than those in the highest intake, and the odds of depression increased linearly with decreasing dietary zinc intake (p=0.004). Similarly, women using supplemental zinc were less likely to have depressive symptoms than non-users (p=0.03). Thus among women, the observed interaction between zinc intake and antidepressant use was consistent with preliminary trials showing the beneficial effects of zinc as an adjunct to antidepressant therapy in treatment-resistant patients [15, 37] but among men, there were no associations between dietary or supplemental zinc intake and depressive symptoms, nor interactions between antidepressant use and zinc in the likelihood of depression (p=0.44). A limitation of the study by Maserejian et al. (2012) [36] was the cross-sectional nature, which leaves uncertainty as to whether the observed associations represent actual causal relationships between zinc and depressive symptoms. It is possible that depression was accompanied by decreased appetite and therefore decreased overall dietary intakes. A 20-year prospective follow-up study by Lehto et al. (2013) [38] to assess relation of dietary zinc intake and the risk of depression in middle-aged men suggest that a low dietary zinc intake may not longitudinally precede depression in men. Dietary zinc intake may not have relevance for the prevention of depression in middle-aged men with a sufficient dietary zinc intake. Since the study sample was comprised exclusively of men, these observations may not be generalizable to women. Overall, our study failed to show any significant efficacy of zinc supplementation to antidepressant medication in improvement of severity of depression which is consisted with few earlier studies. [30,31,36,38]

Relation of serum zinc with depression and effect of zinc supplementation on serum zinc:

Our study did not result in any significant change in serum zinc over time from baseline to 8 weeks in both groups. Neither any significant group*time interaction effect was found for serum zinc level (p=0.831).Earlier studies revealed that major depressive disorder was accompanied by decreased serum zinc concentrations, which corresponded to the severity of depressive symptoms, suggesting that depression alters zinc homeostasis. [13,14,16,39] Since then, various studies have found that serum zinc was significantly lower during acute depressive episodes, and furthermore that levels were normalized after successful antidepressant pharmacotherapy. [15,29] To add to this, a recent case control study by Styczeń et al. (2017)[40] also has confirmed the correlation between zinc deficits present in the depressive episode and

are consistent with most of previous studies. Though there was no significant difference in serum zinc level between depressed patients and healthy controls and between depressive episode and remission, significant difference for serum zinc level was found between patients with and without presence of drug resistance. But our finding is consistent with few earlier studies.[31,35,41-44] Reasons of these inconsistencies have been rightly discussed in a recent meta-analysis [45] where need for prospective cohort studies to establish direction of causation between zinc and depression, if any has been pointed out. The possibility that depression might cause lower zinc concentrations warrants discussion, particularly because appetitive changes are a common component of depression. In line with this, earlier studies have shown trend between lower zinc concentrations and weight loss and anorectic symptoms,[14] suggesting that zinc deficiency could be related to dietary changes; however, this might be argued as zinc deficiency has been found to cause decreased appetite.[46] Supplementation trials might be therefore most appropriate to establish the direction of causation. Also, earlier studies did not report sufficient detail about demographic data; diet and alcohol use.[45] It should also be considered that common depression comorbidities such as alcohol dependence and cardiovascular disease might contribute to lower zinc status in depressed populations. [47-49]

Our study suffered from few limitations. Sample size was small. Though both groups received TAU and thereby did not receive controlled antidepressant medications, we claim that keeping TAU in both groups was an advantage of our study in regard to examine effectiveness of zinc supplementation in our study. Though adding a placebo in TAU group would have added certain advantage of our study, we discussed its limitations too.

Although there was significant improvement in both groups for severity of depression over the period of two months, our study failed to show efficacy of zinc supplementation on severity of depression in patients of unipolar depression. Although baseline serum zinc levels were significantly low in both groups, our study did not show any significant differences in serum zinc level with improvement in severity of depression. Future studies should include a larger sample size, controlled for antidepressant treatment and should have healthy control group with prospective cohort design.

Table 1 Comparison Of Socio-demographic Profile Between Groups.

Variables		TAU + Zn (N=30) n (%)	TAU (N=30) n (%)	χ^2/f/t/U	df	p
Sex	Male	20 (66.6%)	20 (66.6%)	0.00	1	1.00
	Female	10 (33.4%)	10 (33.4%)			
Religion	Hindu	24 (80%)	27 (90%)	1.18f	1	0.28
	Others	6 (20%)	3 (10%)			
Marital status	Married	14 (46.6%)	20 (66.6%)	2.44	1	0.12
	Unmarried	16 (53.4%)	10 (33.4%)			
Occupation	Employed	1 (3.3%)	1 (3.3%)	0.00f	1	1.00
	Unemployed	29 (96.7%)	29 (96.7%)			
Habitat	Rural	23 (76.7%)	24 (80%)	0.09	1	0.75
	Urban	7 (23.3%)	6 (20%)			
Family type	Nuclear	21 (70%)	19 (63.3%)	0.30	1	0.58
	Joint	9 (30%)	11 (36.7%)			
Age (years)	Mean + SD	28.83 ±6.61	33.37±10.69	-1.98t	58	0.053
Education (years)	Mean + SD	9.67±4.36	9.10±3.69	0.54t	58	0.34
Family income/Mth (rupees)	Mean + SD	8816.67 ±8736.05	7933.33 ± 8947.37	415.50U	58	0.61
	Mean rank	31.65	29.35			
	Sum of rank	949.50	880.50			

χ2 - Chi-square test; f Fisher's exact test, t-Independent samples t- test test, U-Mann Whitney's U test. **df-** degrees of freedom. Level of significance accepted at p value of 0.05. TAU – Treatment as usual

Table 2 Comparison Of The Clinical Profiles Between The Two Study Groups.

Variables		TAU + Zn (N=30) n (%)	TAU (N=30) n (%)	χ^2/f/t	df	p
Diagnosis	**Depressive episode (F32)**	10 (33.3%)	9 (30%)	0.08	1	0.78
	R.D.D. (F33)	20 (66.7%)	21 (70%)			
Treatment status	**Drug naive**	6 (20%)	6 (20%)	0.00	1	1
	Drug free	24 (80%)	24 (80%)			
Past medical illness	**Insignificant**	29 (96.7%)	27 (90%)	1.07^f	1	0.30
	Significant	1 (3.3%)	3 (10%)			
Family H/O psychiatry illness	**Absent**	19 (63.3%)	18 (60%)	0.07	1	0.79
	Present	11 (36.7%)	12 (40%)			
Family H/O medical illness	**Absent**	22 (73.3%)	21 (70%)	0.08	1	0.77
	Present	8 (26.7%)	9 (30%)			
Personal history	**Insignificant**	29 (96.7%)	28 (93.3%)	0.35^f	1	0.55
	Significant	1 (3.3%)	2 (6.7%)			
Physical examination	**Insignificant**	28 (93.3%)	27 (90%)	0.22^f	1	0.64
	Significant	2 (6.7%)	3 (10%)			
Baseline zinc level range	**Low**	20 (66.7%)	24 (80%)	1.36	1	0.24
	Normal	10 (33.3%)	6 (20%)			
Age of onset (years)	**Mean ± SD**	23.60±5.08	26.20±10.16	**-1.25^t**	58	0.22
Duration of illness (years)	**Mean ±SD**	5.31 ± 4.91	7.22 ± 7.14	388^U	58	0.36
	Mean rank	28.43	32.57			
	Sum of rank	853	977			

Legends- χ^2 - Chi-square test; f- Fisher's exact test, t-Independent samples t- test test, U-Mann Whitney's U test. **df-** degrees of freedom. Level of significance accepted at p value of 0.05. TAU – Treatment as usual

Table-3 Main effects of time (baseline, 2, 4 and 8 weeks), group and time*group interaction within and between the two groups on various outcome scales for severity of psychopathology:

CLINICAL SCALES		Mean ± SD		Effect	Pillai's trace/ Greenhouse - Geisser F	p	Partial eta squared	Observed power
		TAU + Zn (N=30)	TAU (N=30)					
HAM-D	BASE	29.77±4.28	29.40±4.56	Time	**511.517**	**0.000**	**0.965**	**1.000**
	WK (2)	19.60±5.33	17.73±6.62	Group	0.212	0.647	0.004	0.074
	WK (4)	10.87±6.16	11.23±4.93	Group*Time	1.090	0.353	0.018	0.281
	WK (8)	6.20±3.36	6.30±2.76					
BDI	BASE	39.83±7.08	38.57±7.05	Time	**348.090**	**0.000**	**0.949**	**1.000**
	WK (2)	24.73±7.16	24.00±8.52	Group	0.115	0.736	0.002	0.063
	WK (4)	14.00±6.67	14.27±6.70	Group*Time	0.309	0.781	0.005	0.104
	WK (8)	8.20±6.15	8.03±3.80					
BSSI	BASE	14.33±6.17	14.47±5.64	Time	**111.983**	**0.000**	**0.857**	**1.000**
	WK (2)	4.93±4.25	5.37±5.22	Group	0.004	0.951	0.000	0.050
	WK (4)	1.67±2.04	1.37±1.94	Group*Time	0.204	0.808	0.004	0.081
	WK (8)	0.70±1.26	0.27±0.64					
HAM-A	BASE	26.07±4.58	25.60±5.65	Time	**248.255**	**0.000**	**0.930**	**1.000**
	WK (2)	16.83±4.19	15.93±5.71	Group	0.033	0.856	0.001	0.054
	WK (4)	10.60±4.17	11.07±4.65	Group*Time	0.621	0.558	0.011	0.159
	WK (8)	6.90±3.67	7.10±3.25					

Legends- **HAM-D** Hamilton rating scale for depression; **BDI** Beck depression inventory; **BSSI** Beck scale for suicidal ideation; **HAM-A** Hamilton rating scale for anxiety. Level of significance accepted at p value of 0.05. TAU – Treatment as usual

Table-4Main effects of time (baseline, 2, 4 and 8 weeks), group and time*group interaction within and between the two groups on serum zinc level.

variables		Mean ± S.D.		Effect	Pillai's trace/ Greenhouse –Geisser F	p	Partial eta squared	Observed power
		TAU + Zn (N=30)	TAU (N=30)					
SERUM ZINC	BASE	55.24±14.54	48.69±12.68	Time	1.565	0.208	0.077	0.390
	WK(2)	55.46±16.25	50.96±13.22	Group	2.775	0.101	0.046	0.374
	WK(4)	53.90±16.21	50.30±11.78	Group*Time	0.259	0.831	0.004	0.096
	WK(8)	57.34±15.54	51.99±13.15					

Level of significance accepted at p value of 0.05. TAU – Treatment as usual

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