ORIGINAL ARTICLE

Positive therapeutic and neurotropic effects of yoga in depression: A comparative study

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ABSTRACT

Context: Therapeutic effect of yoga in depression is recognized. Neuroplastic effects of antidepressant therapies are inferred by elevations in brain-derived neurotrophic factor (BDNF). Role of yoga in both these effects has not been studied.
Materials and Methods: Non-suicidal, consecutive out-patients of depression were offered yoga either alone or with antidepressants. The depression severity was rated on Hamilton Depression Rating Scale (HDRS) before and at 3 months. Serum BDNF levels were measured at the same time points. Repeated-measures analysis of variance was performed to look at change across groups with respect to HDRS scores and BDNF levels over 3 months of follow-up. Relationship between change in serum BDNF levels and change in HDRS scores was assessed using the Pearson's correlation coefficient.
Results: Both yoga groups were better than drugs-only group with respect to reduction in HDRS scores. Serum BDNF rose in the total sample in the 3-month period. This was not, however, different across treatment groups. There was a significant positive correlation between fall in HDRS and rise in serum BDNF levels in yoga-only group (r=0.702; P=0.001), but not in those receiving yoga and antidepressants or antidepressants-alone.
Conclusions: Neuroplastic mechanisms may be related to the therapeutic mechanisms of yoga in depression.

Key words: Antidepressant, brain-derived neurotrophic factor, depression, neuroplasticity, yoga

INTRODUCTION

There has been a consistent, on-going search into the biological basis of depression. While the monoamine hypothesis has often been implicated in the pathophysiology of depression.[1,2] decreased neuroplasticity in the hippocampus has recently gained importance as a likely factor in the pathogenesis of depression.[3] This may also explain the relationship between stress and depression.[4]

Brain-derived neurotrophic factor (BDNF) is a key modulator of neuroplastic changes and has been implicated in the pathophysiology of depression[5] through the stress pathway.[6,7] Decreased serum BDNF levels were observed in drug free patients with depression in comparison with the healthy controls[8,9] and serum BDNF level has been shown to increase with antidepressant treatment.[10-12] A recent study showed serum BDNF levels were significantly correlated with hippocampal volume in moderately depressed patients.[13] Hence, abnormal neuroplasticity has been proposed as an important pathophysiological mechanism underlying depression.[14]

For less severe depression, antidepressant therapy or psychotherapy or complementary and alternative

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systems of medicine treatment could be used as a first line treatment.[15] Reviews endorse a role for yoga in depression.[16,17] Most of the studies have used only a few yoga practices for treating depression either breathing exercises or different Āsanā practices or only meditation.[18-20] In this study, we have used a generic yoga module developed from traditional texts and validated by the yoga experts as a treatment for depression (Naveen *et al*., in this issue). Yoga has been shown to have a significant effect on brain neurotransmitters such as gamma-Aminobutyric acid, indicating its potential usefulness in treating depression and anxiety disorders.[21] Further, yoga therapy can improve cognitive functions, which is one of the indicators of neuroplasticity.[20,22]

We examined in patients with depression the therapeutic effects of yoga as well as its effects on serum BDNF. We also examined the relationship between the antidepressant and neurotropic effects (rise in BDNF) with yoga and medications.

MATERIALS AND METHODS

Subjects

The study subjects came from yet another larger study comparing clinical effects of yoga-only with either medication-only or a combination.[23] A three-group, single blind comparative trial design was used in this study. Depressive disorder patients attending out-patient services with a score of 11 or more on Hamilton Depression Rating Scale (HDRS) and score of 2 or less on the suicide item of HDRS[24] were recruited after screening by the researcher Naveen GH and a psychiatry resident (Mukund G. Rao. Patients were aged between 18 and 55 years. A psychiatrist made clinical diagnosis of depressive disorder using the mini international neuropsychiatric interview (MINI);[25] a psychiatry resident trainee also reached a Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) diagnosis of depressive disorder in these patients.[26] Out of the 137 patients, 101 were medication-naïve and 36 were medication-free for at least 1 month. Patients with mental retardation, substance abuse disorders (except nicotine and caffeine), organic disorders such as dementia, epilepsy or cerebrovascular accidents, history suggestive of psychosis or bipolar disorder, or having suicidal risk or catatonia were excluded from the study. None had received yoga as treatment before. Patients did not have any indications for electroconvulsive therapy (i.e., catatonia/ severe depression). Written informed consent to take part in the study was obtained. The study was approved by the Institutional Ethics Committee. The option of yoga therapy, either alone or in combination with medication or medication alone, was offered to patients. There were three naturalistic groups of patients: Medication-alone (n=78); yoga therapy-alone (n=23) and medications + yoga therapy (n=36). The duration of the follow up was 12 weeks.

Yoga therapy module

The construction and description of the yoga module is described separately elsewhere.[27] The module is available on request with the authors.

Yoga procedure

The participants of the yoga + antidepressant therapy and yoga therapy-alone groups were requested to come daily for a period of 10 days to the National Institute of Mental Health and Neurosciences, where a yoga professional taught them the yoga practices. Each session of training/ practice lasted 1 hour. The participants were then asked to come to perform yoga in the yoga therapy center once a week for the next 2 weeks. The subjects were instructed to continue yoga at home thereafter, but attend one booster training session in the yoga therapy center at the end of the next 2 months. Home practices were monitored by a family member. They were also instructed to maintain a register to document the duration of each day's yoga at home.

Antidepressant medication

During 3 months of the study period, the patients on antidepressant medications received consultation with their respective psychiatry consultants. The antidepressant type and dose were chosen by these consultants. This treatment remained unchanged in nearly all patients. Antidepressants administered were escitalopram (10-15 mg/day), fluoxetine (20-40 mg/day), duloxetine (60 mg/day), sertraline (50-100 mg/day), amitriptyline (25-100 mg/day) and mirtazapine (7.5-15 mg/day).

The researcher had a telephonic conversation with all the subjects at different time points during the 3 months of treatment to encourage compliance to medication/yoga practice.

Assessments

A rater trained in psychiatry for 18 months and blind to the group status of the patients (psychiatry resident) rated the severity of depression using the HDRS and clinical global impression (CGI) (baseline and 3 months thereafter).[28]

Assessment of neurotrophin levels (At baseline and at 12 weeks): Venous blood was sampled between 8:30 am and 11 am before breakfast at baseline and 12 weeks thereafter. The sample was allowed to clot and the serum was separated within 30 min. Coded serum samples were stored at −80°C. The BDNF assay was performed in batches within a period of 3 months from the beginning of the sample collections. Analysis was performed with the help of biochemist using the enzyme-linked immunosorbent assay with commercial kits (Ray Biotech Inc.,Wembley, Middlesex, UK) according to the manufacturer's instructions. The intra- and inter-assay coefficient of variations was 1.34% and 4.34%, respectively.

Statistical analysis

The sample for statistical analysis consisted of only those who had both clinical (HDRS and CGI) and BDNF data at baseline and after 3 months (12 weeks). The demographic and baseline clinical profile were compared between three groups using Chi-square test and analysis of variance. Two-way repeated-measures analysis of variance (RMANOVA) was used to examine the change in HDRS, CGI and BDNF over two assessments. Pearson's correlation coefficient was computed to examine the relations between fall in HDRS (pre - post) and rise in BDNF (post - pre). For significance, alpha was fixed at $P<0.05$.

RESULTS

Only 62 patients were available for assessments at the time points required for this study (yoga-alone=19; yoga with medications=22; only medications=21). The three groups were not different with respect to baseline socio-demographic details, illness and other parameters except education; patients choosing yoga had higher education [Table 1].

There was a significant drop in depression scores over time across all groups ([Table 2]; RMANOVA occasion effect: $F=271.7$; $df=1, 59$; $P<0.001$); patients receiving yoga therapy had greater improvement than those receiving medications only (group effect: $F=5.7$; $df=2, 59$; $P=0.005$; group X occasion interaction effect: $F=6.2$; $df=2, 59$; $P=0.004$). CGI severity score showed similar results (occasion effect: $F=369.6$; $df=1, 59$; $P<0.001$; group effect: $F=12.4$; $df=2, 59$; $P<0.001$; group X occasion effect: $F=10.5$; $df=2, 59$; $P<0.001$). With respect to serum BDNF levels, the occasion effect ($F=4.5$; $df=1, 59$; $P=0.039$) and group effect ($F=4.1$; $df=2, 59$; $P=0.02$) were significant; group X occasion effect was, however, not significant ($F=0.14$; $df=2, 59$; $P=0.87$).

In the total sample, drop in HDRS and rise in BDNF were not correlated ($r=0.1$, $P=0.5$). The correlation was not significant in medication only ($r=-0.15$; $P=0.5$) as well as in medication plus yoga ($r=-0.11$; $P=0.62$) groups. However, in the yoga-only group, there was a high correlation between the decline in HDRS and rise in BDNF levels ($r=0.7$, $P=0.001$).

DISCUSSION

Our study showed that there was a significant reduction in HDRS scores at follow-up in patients with depression in all three groups. Patients receiving yoga with or without anti-depressants had a greater reduction in depression scores than antidepressant alone. A previous study had reported Sudarshan Kriya Yoga to have equivalent antidepressant efficacy to imipramine.[18] The remission rate in our study was 59.9% and previous studies have shown rates ranging from 23.52% to 100%.[8,11,12,19,29-32] There was a significant increase in BDNF levels at follow-up as indicated by significant within subject occasion effect. However, there was no occasion X group interaction, suggesting that the change in BDNF was not different across the three groups.

In the entire group, there was no correlation between change in BDNF levels and that in HDRS scores. This is consistent with studies,[10,11,30,31] which have examined this issue earlier. There was a significant positive correlation between change (reduction) in HDRS and change (rise) in serum BDNF levels in yoga-only group ($r=0.7$; $P=0.001$). This was not so in those receiving antidepressants (either with or without yoga). Antidepressant medications may have a direct influence on serum BDNF levels,[8,10,31,33] thus confounding the relationship between change in depression score and that in BDNF levels. This confound was absent in yoga-only group. It may be noted that dose and type of antidepressant were not controlled. It is possible that the finding of such a correlation in the yoga-only group could be related to the absence of the medication confound. Yoga may have different biological mechanisms that operate on both antidepressant and BDNF elevation pathways. Stress reduction mechanisms, by way of quieting the hypothalamic-pituitary-adrenal (HPA) axis, may be particularly relevant to the effect of yoga in reducing

Table 1: Demographic and illness characteristics

Parameter	Yoga-only (*n*=19)	Yoga+medication (*n*=22)	Medication-only (*n*=21)	F/χ^2	*P*
Mean (SD) age in years	35.9 (7.8)	33.6 (10.3)	32.4 (7)	0.83	0.44
Male:Female	12:7	12:10	12:9	0.32	0.85
Mean (SD) education in years	12.8 (3.4)	11.4 (4.4)	9.1 (4.9)	3.87	0.03
Mean (SD) duration of illness in months	22.4 (26.3)	19.7 (22.9)	21.8 (20.8)	0.78	0.93
Drug naïve (%)	11 (57.9)	15 (68.2)	15 (71.4)	0.88	0.64
Family H/o depression (%)	4 (21.1)	6 (27.3)	4 (19)	1.98	0.74
Patients regular/compliant (%)	14 (73.7)	16 (72.7)	11 (52.4)	2.68	0.26
Medications (%)					
Fluoxetine	-	4 (18.2)	4 (19)	2.11	0.55
Escitalopram	-	16 (72.7)	14 (66.7)		
Amitriptyline	-	1 (4.5)	3 (14.3)		
Mirtazepine	-	1 (4.5)	0 (0)		

SD – Standard deviation

Table 2: Outcome variables at baseline and at 3-months across the three groups

Measure	Yoga-only (*n*=19)	Yoga+medication (*n*=22)	Medication-only (*n*=21)
Mean (SD) HDRS			
Baseline	16.8 (4.1)	18.3 (5.3)	18.1 (4.4)
3-months	2.8 (2.8)	4.8 (5.6)	9.8 (5.7)
Mean (SD) CGI			
Baseline	4.1 (0.5)	4.4 (0.5)	4.3 (0.5)
3-months	1.3 (0.4)	1.7 (0.8)	2.4 (0.0)
Mean (SD) BDNF*			
Baseline	20.3 (6.6)	16.9 (5.8)	21.2 (5.6)
3-months	21.4 (6.6)	18.8 (5.8)	23.3 (5.9)

*Measured in ng/ml; HDRS – Hamilton depression rating scale; CGI – Clinical global impression; BDNF – Brain-derived neurotrophic factor; SD – Standard deviation

depression. This is a first study, which looked at the changes in serum BDNF levels after yoga.

We used a yoga-therapy module rigorously validated for use in patients with depression. Patients with suicidal risk were not recruited due to ethical reasons. None of the patients except two received any other form of intervention that could have altered the depression outcome, such as supportive therapy/cognitive behavior therapy. The raters being blind to the allocation status of the patients avoided any possible bias in the assessments. We used a standardized diagnostic tool, the MINI[25] to diagnose depressive disorder. Further, antidepressant drugs and dosages used in this study are according to the standard treatment algorithms.[34] Assessment of serum BDNF level was performed by a biochemist who was blind to the treatment status of the patients. Standard procedure was followed to collect and store the serum samples. It is known that BDNF being a small peptide is sensitive to climatic changes; BDNF concentrations are also related to platelet BDNF release.[9]

Non-random allocation to treatment groups is a major limitation of this study. The three groups were not different with respect to baseline socio-demographic details, illness and other parameters. Hence, the possibility of bias due to baseline differences is small. Nevertheless, we cannot rule out the possibility of differences in unmeasured variables influencing the outcome measures. The dropout rate from the study is substantial (close to 50%). This is not surprising as patients were not severely depressed; yoga practice too has several barriers leading to attrition.[35] A few other limitations are worth mentioning. This study had a single-blind design where the rater was blind to the treatment status of the patients, but the latter were aware about their treatments. Hence, we cannot rule out the possibility of awareness about the treatment having an influence on the outcome. Theoretically, use of "placebo-yoga" could have resulted in unbiased assessment of the outcome measures. However, "placebo-yoga" is not possible because, the general public is aware of yoga techniques in India. Hence, placebo-arm and double-blind design pose a challenge in yoga research.[36] Further, attrition rate was about 35.76%. This is a problem associated with such studies in depression: Dropout percentages in earlier studies have ranged from 13% to 55%.[11,19,29,37-39]

The interactions of BDNF with serotonergic systems, HPA axis and other biological markers have been extensively studied.[40,41] An important issue is whether serum BDNF levels are related to brain BDNF levels. It may be noted that BDNF crosses blood brain barrier and hence serum BDNF reliably reflects brain BDNF concentrations.[42] Pre-clinical studies in rats have shown a positive correlation between serum and cortical levels.[43] Future studies could look to explore the relation between serum BDNF levels and cerebrospinal fluid BDNF levels in patients with depression. Association between BDNF levels and volumetric changes in the hippocampus may be worth exploring as it is evident that patients with depression have decreased hippocampus volume.[44]

Though significant statistically, the magnitude of BDNF change detected in this sample was small. Furthermore, the differences obtained in therapeutic effects by the interventions were not seen in the BDNF responses. This leads to a suspicion if the two are related at all. The only argument in this favor comes from the observed direct correlation of antidepressant effects and BDNF elevating effects in the yoga-alone group. This calls for more research. Alternative tropic mechanisms such as changes in the vascular endothelial growth factor levels[45,46] in the serum deserve examination.

In summary, yoga alone produced substantial antidepressant effects that correlated with the elevation serum BDNF levels. The findings argue for a neuroplastic mechanism of antidepressant action for yoga. The limitations of the study weaken this argument and point the need to investigate other tropic mechanisms.

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