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Original Research Article

Efficacy of Brahmi vati in generalised anxiety disorder — Randomized double blind comparative clinical trial

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ABSTRACT

Background: Generalized Anxiety Disorder (GAD) is the most common anxiety disorder. GAD has high comorbidities and it can affect social, professional and personal life. Ayurvedic medicine, Brahmi vati is explored for the possible role in management of GAD and is compared to Manasmitra vataka.
Aim: To evaluate the efficacy of B. vati on Generalized Anxiety Disorder.
Methods: A randomized double blind controlled trial, with total 56 patients meeting the DSM V criteria of GAD between 20—60 years of age and either sex participated in the study. Participants were randomly divided into two groups, Brahmi group received capsule B. vati 500 mg and Manasmitra group received capsule M. vataka 500 mg thrice a day with water for 45 days. Assessments were conducted through various clinical parameters such as Hamilton Anxiety Rating Scale (HARS), GAD 7 scale (GAD 7), Beck Depression Inventory scale (BDI), Epworth sleepiness scale (ESS), Pittsburgh Sleep Quality Index (PSQI), WHO Quality of Life- BREF (WHOQOL-BREF), Clinical Global Improvement scale (CGI). Blood variables including Haemoglobin, Erythrocyte Sedimentation Rate (ESR), Liver Function Test (LFT) and serum creatinine were assessed before and after the study. Assessments during intervention were conducted on every 15th day.
Results: Study results indicate that both B. vati and M. vataka were comparable and each produced significant improvement (p < 0.001) in HARS, GAD-7, BDI, ESS, PSQI, WHOQOL-BREF and CGI. Brahmi vati also produced significant decrease in systolic (p = 0.002) and diastolic (p < 0.001) blood pressure. Both groups showed good safety profile evaluated through the assessment of serum creatinine levels and LFT.
Conclusion: B. vati and M. vataka were effective, safe and comparable in the management of GAD. Warrants further studies.

1. Introduction

Generalized Anxiety Disorder (GAD) is a one of the most common and disabling anxiety disorder. Predominant symptoms are excess worry, restlessness, reduced concentration, irritation, insomnia and muscle tension [1]. Major presentation of GAD is the excess, constant worry about day-to-day activities and minor events.

Asian studies on GAD have shown, life time prevalence has increased from 0.9% (2010) to 1.6% (2016) [2] and 12-month prevalence is 0.6% [3]. Prevalence of GAD is higher in western countries like Canada, where life time prevalence is 8.7% and 12 month prevalence is 2.6% [4]. Indian study reported 3—3.5% prevalence of anxiety disorders in adulthood. Contribution of Disability adjusted life years (DALYs) due to anxiety disorders among mental disorders in 2017 was 19% in India [5]. It manifests with various comorbidities including depression, insomnia, substance abuse, anxiety disorders, personality disorders and chronic medical illness such as hypertension and diabetes. Comorbidities contribute to the poor treatment outcomes [6]. Usually 60% have comorbidities with Major Depressive Disorder and other anxiety disorders [7]. Comorbidity diagnosis is associated with more social and occupational disturbance [8]. GAD is associated with greater

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reliance on public assistance, impaired work productivity, disturbed social relationships and low ratings of satisfaction in life [9] and has a gross impact. GAD patients (27%) suffered loss of 4.6 work days because of disability in the previous month and with comorbid depression, 59% of patients lost 8 work days [10]. As GAD patients present with physical symptoms leading to substantial use and burden on health care services. Pathophysiology of GAD is contributed by various biological factors like genetics, neurobiological and psychological factors. Psychological derangements are cognitive behaviour, information procession, affect and psychodynamic components. Psychosocial components like development, environment also pay a role. Neurobiological factors include decreased Gamma-aminobutyric acid (GABA) and serotonin levels, increased concentration of noradrenergics, derangements in neural circuitry and endocrine system.

Treatment seeking among GAD patients is low i.e. only 40% [11]. Management of GAD is through various pharmacological agents. They include serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors (SNRI), benzodiazepines, azapirones and pregabalin. A meta analysis [12] reported that the drug therapy in GAD has low to moderate effect size. SSRI's are considered as the first line pharmacotherapy in anxiety disorders [13]. Inspite of advances in management of GAD, full or partial remission in long term (5 yrs or more) is estimated in only 38−41% of the cases [8]. Few of the limitations of first line conventional medications are poor efficacy, lack of response in many patients, 2−4 weeks delay in onset of symptom relief, slow response, lack of full remission and presence of residual symptoms and risk of relapse [14]. SSRI and SNRI have various adverse effects including nausea, gastrointestinal problems, sexual dysfunction, headache, sweating, weight gain and blood pressure changes [15]. Abrupt discontinuation of these can lead to discontinuation or withdrawal symptoms [16]. All these limitations are encouraging the patients to explore for possible therapies in complimentary and alternative systems of medicine. Anxiety (OR, 3.1; 95% CI, 1.6−6.0) is one of the strongest predictor for the use of alternative system of medicines [17].

Mental health and psychiatric management has been elaborately dealt in *Ayurveda*. In *Ayurveda Chittodwega* is considered as one of the psychiatric disorder [18], caused due to impairment in *Manasika dosha* including *Raja*s and *Tamas. Chittodwega* is similar to GAD in terms of manifestations and etiopathology. One of the widely studied drug among Complimentary and Alternative therapy is *Kava* (*Piper methysticum*) and it has shown efficacy in management of GAD [19]. A meta analysis reported Complimentary and Alternative therapy (*kava−kava* and homeopathy) compared to placebo had negative effect size [12], suggesting it to be inferior to placebo. Due to multiple hepatotoxicity reports it was banned in UK and has limited use. A study [20] has highlighted the role of *Manasmitra vataka* (*Ayurveda* medication) in GAD with comorbid social phobia. Ethanolic extract of *Aswagandha* (*Withania somnifera*) in patients with ICD-10 anxiety disorders resulted in better improvement compared to placebo [21]. Therapeutic massage therapy had beneficial effect in GAD and was comparable to thermotherapy and relaxation room therapy [22]. However *Ayurveda* medications in GAD remains to be under explored. *Brahmi vati* is one of the commonly used *Ayurveda* medication by *Ayurveda* clinicians in management of anxiety disorders. *Ayurveda* texts advocate *Manasamitra vataka* to be helpful in various psychological, psychiatric disorders and epilepsy [23]. *Brahmi vati* have various ingredients that have psychotropic, nootrophic effects. *Brahmi vati* has utility in various psychiatric disorders and has intellect and memory promoting effects [24]. Hence study was planned to evaluate the efficacy of *Brahmi vati* in GAD.

2. Materials and methods

Patients attending the outpatient department of KLEU Shri B M K *Ayurveda* Hospital were recruited in the study. CONSORT statement guidelines [25] have been followed in reporting the trial.

2.1. Patients

Patients (n = 56) diagnosed as Generalized Anxiety Disorder as per DSM V criteria [26]were recruited from outpatient department of KLE's Shri B M K *Ayueveda* Hospital, Belgaum, Karnataka. India.

2.1.1. Inclusion criteria
Patients of either sex between the age of 20−60 years, fulfilling DSM V diagnostic criteria for GAD were included in the study.

2.1.2. Exclusion criteria
Patients with *lakshanas of Unmad* (co-morbid psychiatric disorders); on psychotropic drugs four weeks prior to study; substance abuse like alcohol etc.; significant depression (BDI >17); other medical complications like hypertension, diabetes mellitus; pregnant and lactating women were excluded from the study.

2.1.3. Screening methods
The 56 patients were recruited in the study. They were examined thoroughly and the data was recorded systematically. Laboratory investigations including haemoglobin, white blood cells-total count, differential count, erythrocyte Sedimentation Rate (ESR), liver function test and serum creatinine were carried out in the clinical laboratory of KLEU Shri BMK *Ayurveda* hospital Belgaum, at baseline and 45th day of intervention in each patient.

2.2. Research design

The study was a Randomised double blind, comparative clinical study. Block randomization allocation was done with 28 blocks of 2. The patients were allocated in control and intervention groups in 1:1 ratio. PI was responsible for sequence generation and sealing. Allocation concealment was done through sealed opaque envelopes. Computer generated random numbers were utilized for the study. All investigators were blinded to the allocation. The scholars involved in randomisation, distribution and administration of study articles were independent from investigators. All participants, investigators, outcome assessors were blinded. Unblinding happened after the data analysis were complete. Adherence was assessed by counting number of unused capsules on every 15th day by one of the investigators. Outcome variables were assessed by the investigators at all the assessment time points. Sample size was calculated based on a previous study [20]. Primary outcome of this study was used to calculate sample size. Total Sample was 56, 28 in each arm with 5% alpha error and 80% power.

2.2.1. Intervention
All the patients were randomly divided into two groups: *Brahmi* group and *Manasmitra* group. *Brahmi* group (n = 28) received *Brahmi vati* capsules 500 mg TID with water after food, while *Manasmitra* group (n = 28) received *Manasmitra vataka* capsules 500 mg TID with water after food. Both the interventions and their dosage were as per the classical text books of *Ayurveda*. The ingredients of *Brahmi vati* were procured from authentic distributors. Authentication of all raw material were done at Central Research Facility (CRF) KLE BMK *Ayurveda Mahavidyalaya*, Ministry of AYUSH, Government of India approved *Ayurveda, siddha and Unani*

(ASU) drug testing laboratory. Qualitative analysis of each raw material and finished product as per API (*Ayurvedic Pharmacopeia of India*) guidelines were done. Qualitative Analysis of raw drugs were in terms of ash, extractive values and loss on drying. Qualitative analysis of finished product were in terms of ash values and loss on drying. Capsule filling of *Brahmi vati* powder was done as per standard procedures in GMP approved KLE *Ayurveda* Pharmacy, Belgaum. *Manasmitra vataka* in tablet form was procured free of cost from *PAKRUTI* Pharmacy, Karwar, India and capsule filling was done as per the standard procedures in GMP approved KLE *Ayurveda* Pharmacy, Belgaum, Karnataka, India. Duration of intervention was 45 days with follow-up on every 15th day during treatment. The nature and design of the study were explained to patients, and informed consent was obtained. The study was approved by the Institutional Ethics Committee (Protocol Id BMK/17/PG/KC/4, KLEU BMK *Ayurveda Mahavidyalaya* Belagavi, Date of Approval 20.03.2018. CTRI Registration Number CTRI/2018/07/014711). Data collection was from February 2019 to March 2020. During the study, patients were asked to adhere to the treatment protocol and report any adverse events to the investigators at the earliest. Any manifestations either existing or new during the course of intervention that cause considerable distress were screened for possible adverse events.

2.3. Criteria for assessment

2.3.1. Primary outcome measure
Hamilton Anxiety Rating Scale (HARS) [27].

2.3.2. Secondary outcome measure
The secondary outcomes measures were GAD 7 scale [28], Beck Depression Inventory scale (BDI) [29], Epworth sleepiness scale (ESS) [30], Pittsburgh Sleep Quality Index (PSQI) [31], WHO Quality of Life- BREF (WHOQOL-BREF) [32], Clinical Global Improvement scale (CGI) [33], hemoglobin, WBC-total count, differential count, erythrocyte sedimentation rate (ESR), liver function test and serum creatinine.

All the clinical assessment scales were evaluated at baseline, 15th, 30th and 45th day. Blood assessments were done at base line and 45th day of interventions.

2.4. Statistical methods

Statistical analysis was carried out using SPSS Version 25.0 (IBM Corporation, Chicago, Illinois, United States). Homogeneity of data across the groups was evaluated by the $\chi 2$ test. Comparison of groups across different time points was carried out by two way repeated measure Analysis of Variance (rmANOVA) with Bonferroni post-hoc test. Comparison of within groups at two time points was analyzed by paired T test. Comparison of groups at a time point was through independent sample t test. Effect size was calculated by Partial Eta Square method, effect of treatment through the outcome from baseline to 45th day of treatment were used for assessment. The criteria used for interpreting effect size measures were as follows: 0−0.2 minimal, 0.2−0.5 as small, 0.5−0.8 as medium, and above 0.8 as large effect size [34]. Values are reported as mean ± standard deviation. All tests were considered statistically significant at p < 0.05.

3. Results

A total of 56 patients participated in the study. No patients in either group reported any adverse effects. Two patients from *Manasmitra* group dropped out of the study due to intermittent illness (Fig. 1).

The mean age (p = 0.504), gender (0.05), socio-economic status (0.92), education (0.89), weight (p = 0.948), BMI (p = 0.83), systolic and diastolic blood pressure at base line, duration of illness (p = 0.866) of the patients were comparable in both the groups (Table 1, Table 2) (Fig. 1). Blood parameters including haemoglobin, WBC total count, differential count, ESR, liver function test and serum Creatinine were comparable between the groups at baseline (see Table 3).

3.1. Primary outcome

The study data indicate that improvement in both the groups was comparable in total score of Hamilton Anxiety Rating Scale. Each group showed significant improvement on HARS at all the three time points. Both interventions produced significant reduction (p < 0.001) in total score of Hamilton Anxiety Rating Scale at baseline to 15th day, 30th day and 45th day of intervention. HARS showed significant reduction (p < 0.001) at 15th −30th, 15th −45th and 30th − 45th day of intervention (Table 2).

3.2. Secondary outcomes

Both the interventions were comparable in all secondary outcome variables except in BDI and CGI-Efficacy Index. Post hoc assessment between groups showed insignificant changes in BDI and CGI-Efficacy Index. However, within group comparison showed significant improvement in both the groups in all the clinical assessment parameters. Interventions produced significant linear reduction in GAD-7, BDI, ESS, PSQI, WHO Quality of Life- BREF, CGI-severity, CGI-Global Improvement, CGI-Efficacy index at all three time points in both groups (p < 0.001) (Table 2). Significant reduction was observed in systolic blood pressure (SBP) in both *Brahmi* (p = 0.001) and *Manasamitra* groups (p = 0.03), diastolic blood pressure (DBP) reduction was observed only in *Brahmi* group (p < 0.001). Effect size assessment indicated medium effect in diastolic blood pressure, CGI- Severity favoring *Bramhi vati* and *Manasamitra vataka* groups respectively. Small effect size (0.2) in systolic blood pressure and WHOQOL-BREF were observed. Minimal effect was seen in BMI, HARS, GAD7, BDI, PSQI, ESS, CGI-GI and CGI-EI. Statistically significant changes were not obsrved in blood assessment parameters in comparison. *Manasamitra* group showed no changes in any of the blood parameters including hemoglobin, ESR, total bilirubin, direct bilirubin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Albumin, total protein, Albumin globulin ratio, Alkaline phosphatase and Creatinine. Whereas *Brahmi* group showed improvements in albumin and albumin-globulin ratio only (Table 3).

4. Discussion

The study showed that efficacy of *Brahmi vati* and *Manasmitra vataka* were comparable in the management of GAD. Both drugs decreased anxiety, worry and depression. Improvement was observed in night sleep, day time drowsiness, quality of life, disease severity and global improvement and efficacy. Both the drugs showed no adverse drug reactions/events and had good safety margins as the liver function tests and serum creatinine were within the normative limits both before and after the intervention.

Majority of patients in the study were of middle age (37.7 yrs), female (62%), middle socioeconomic class, non vegetarian diet, graduate level education, married, *vata pittaja and Rajasika prakurti*, mean duration of illness was 3.6 yrs, all had severe anxiety (HARS>24). All were diagnosed for the first time and were not medicated for GAD. Haemoglobin, ESR, liver function tests and
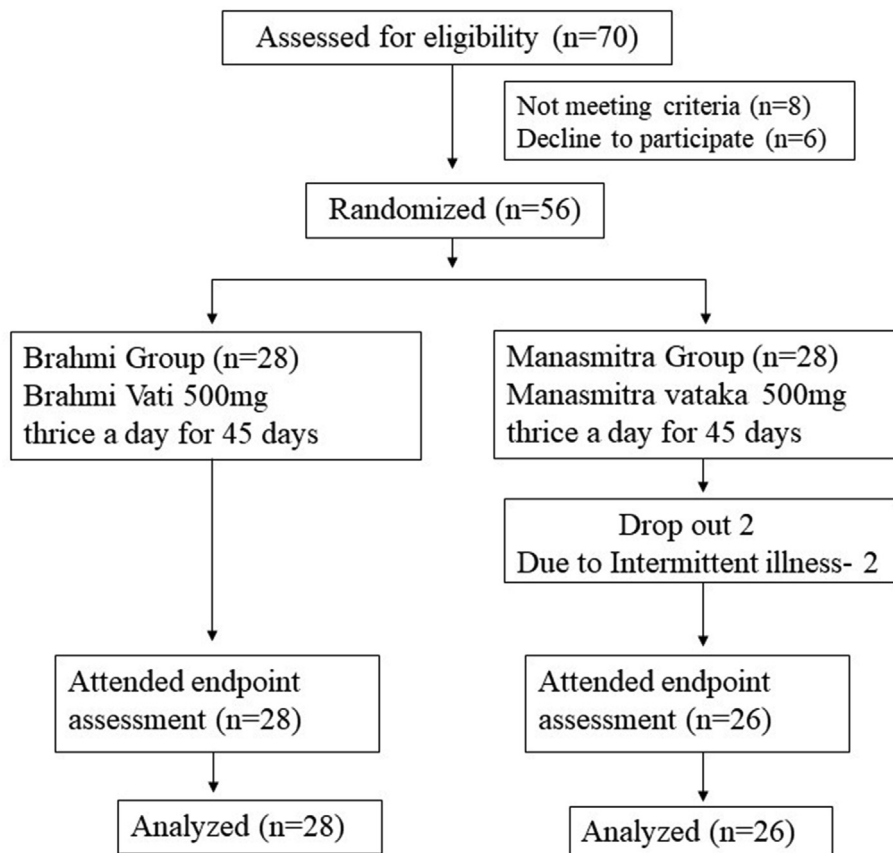
Fig. 1. Subject flow chart through the study.

serum creatinine were within normative range both before and after intervention.

Effect of *Brahmi vati and Manasamitra vataka* in primary, secondary and other outcome variables were comparable. Effect of *Brahmi vati and Manasamitra vataka* on HARS, primary outcome variable were comparable. Both interventions produced significant

and similar decrease of HARS in within group comparison. Similar was the effect on secondary outcome variables like GAD7, BDI, ESS, PSQI, WHOQOL-BREF, CGI-S, CGI-GI, CGI-EI. Both interventions produced significant and similar improvements in worry, depression, daytime sleepiness, sleep profile, quality of life, disease severity, global improvement and efficacy index. In other outcome variables

Table 1
Patient profile at baseline.

Clinical profile		Brahmi Group (n = 28)	Manasamitra Group (n = 28)	p
Age (Yrs, mean ± SD)		38.7 ± 11.0	36.6 ± 11.9	0.50
Gender	Male	14	7	0.05
	Female	14	21	
Socioeconomic Status	Higher class	4	4	0.92
	Middle class	20	21	
	Lower class	4	3	
Diet	Veg	8	8	1
	Non veg	19	19	
Education status	Primary	5	5	0.83
	High school	8	10	
	Graduate	15	13	
Marrital Status	Married	17	18	0.26
	Unmarried	4	7	
	Divorce	4	3	
	Widow	3	0	
Shareerika Prakurti	VataPitta	11	13	0.75
	Vata Kapha	11	10	
	Pitta vata	1	0	
	Pitta Kapha	5	5	
Manasika Prakurti	Rajasika	17	19	0.57
	Tamasika	11	9	
Duration of illness (Yrs, mean ± SD)		3.4 ± 2.4	3.3 ± 2.8	0.86
Study completed		28	26	

Table 2
Effects on outcome variables - Subjective parameters, Blood pressureand and BMI.

Sl.No	Parameters	Intervention	Baseline	15th day	30th day	45th day	P value
Primary Outcomes							
1.	HARS	Brahmi	40.2 ± 5.8	35.1 ± 7.1	28.5 ± 9.4	24 ± 9.8	0.13
		Manasamitra	42.6 ± 6.1	37.9 ± 6.8	30.4 ± 9.1	26.1 ± 9.8	
Secondary Outcomes							
2.	GAD7	Brahmi	18.5 ± 1.7	16.0 ± 2.2	12.4 ± 3.2	9.4 ± 3.2	0.77
		Manasamitra	18.9 ± 1.5	16.1 ± 2.4	12.4 ± 2.7	9.9 ± 3.4	
3.	BDI	Brahmi	14.1 ± 2.2	12.9 ± 2.7	8.8 ± 2.9	5.8 ± 2.9	0.03
		Manasamitra	13.4 ± 2.6	11.7 ± 2.9	7.6 ± 2.7	4.2 ± 2.8	
4.	ESS	Brahmi	14.4 ± 4.2	12.7 ± 3.9	8.2 ± 4.1	6.9 ± 4.1	0.78
		Manasamitra	14.8 ± 5.1	12.8 ± 4.7	8.1 ± 4.6	6.1 ± 4.1	
5.	PSQI	Brahmi	15.1 ± 2.4	12.6 ± 3.0	8.8 ± 3.2	6.4 ± 2.9	0.41
		Manasamitra	14.4 ± 3.8	11.6 ± 3.7	8.6 ± 3.5	6.3 ± 3.3	
6.	WHOQOL-BREF	Brahmi	77.2 ± 7.3	80.3 ± 8.0	86 ± 7.9	87.5 ± 9.2	0.33
		Manasamitra	78.1 ± 8.3	82.2 ± 8.0	87.9 ± 8.7	90.5 ± 8.8	
7.	CGI-S	Brahmi	4.8 ± 0.6	4.2 ± 0.6	3.6 ± 0.7	3.2 ± 0.6	0.16
		Manasamitra	4.8 ± 0.6	4.0 ± 0.6	3.3 ± 0.5	2.8 ± 0.5	
8.	CGI-GI	Brahmi	–	3.6 ± 0.4	2.9 ± 0.4	2.6 ± 0.5	0.10
		Manasamitra	–	3.3 ± 0.5	2.7 ± 0.6	2.3 ± 0.6	
9.	CGI-EI	Brahmi	–	10.3 ± 2.1	7 ± 1.9	5.7 ± 2.1	0.02
		Manasamitra	–	8.9 ± 2.1	5.7 ± 1.9	4.5 ± 2.3	
Other variables							
10.	SBP (mm of Hg)	Brahmi	126.1 ± 10.2	124.6 ± 8.1	121.1 ± 7.8	118.8 ± 7.2	0.55
		Manasamitra	123.7 ± 10.4	122.3 ± 6.7	121.0 ± 7.2	118.4 ± 7.2	
11.	DBP(mm of Hg)	Brahmi	82.1 ± 8.7	80.1 ± 7.1	76.9 ± 6.5	74.2 ± 6.9	0.20
		Manasamitra	76.7 ± 9.6	76.8 ± 7.3	76 ± 6.6	73.9 ± 6.4	
12.	BMI	Brahmi	25.1 ± 5.9	25.1 ± 5.8	25.1 ± 5.7	25.1 ± 5.7	0.58
		Manasamitra	24.3 ± 4.0	24.3 ± 4.0	24.3 ± 3.9	24.3 ± 3.9	

Expressed in mean and standard deviation.
p values respect to baseline are presented.
SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure.

like DBP, showed improvement only with *Brahmi vati* intervention. DBP reduced from prehypertensive stage to normal range. SBP in both groups reduced from prehypertensive stage to normal range. Liver function tests including albumin and albumin globulin ratio showed improvements with *Brahmi vati* interventions, however pre and post values were within the normative ranges. Though effect of interventions on Clinical global impression- Severity score was comparable, however effect size was moderate and favored

improvement with *Manasamitra vataka* intervention. Anxiety levels (HARS) were significantly reduced but levels maintained in severe stage even at the end of 45 days interventions in both groups. But with GAD7, severity decreased form severe stage to moderate stage. Depression (BDI) levels decreased in both the groups from mild to normative ranges. Day time sleepiness reduced form moderate category to near normal day time sleepiness. Night sleep also reduced from poor quality to near normative range. Clinical global

Table 3
Effects on safety variables.

Sl. No	Outcome variable	Intervention	Baseline	45th day	P
1	Hemoglobin (g/dl)	Brahmi	13.2 ± 1.9	13.4 ± 1.7	0.59
		Manasamitra	12.7 ± 1.9	11.7 ± 3.8	
2	ESR (mm in 60 mints)	Brahmi	18.1 ± 9.5	15.5 ± 7.9	0.21
		Manasamitra	17.5 ± 7.5	17.3 ± 7.1	
3	Total Bilirubin (mg/dL)	Brahmi	0.4 ± 0.1	0.4 ± 0.0	0.82
		Manasamitra	0.4 ± 0.1	0.4 ± 0.1	
4	Direct Bilirubin (mg/dL)	Brahmi	0.1 ± 0	0.1 ± 0	0.28
		Manasamitra	0.1 ± 0	0.1 ± 0.1	
5	AST (IU/mL)	Brahmi	24.8 ± 4.7	22.8 ± 4.7	0.16
		Manasamitra	22.5 ± 5.7	23 ± 4.1	
6	ALT (IU/mL)	Brahmi	23.1 ± 5.6	21.5 ± 5.0	0.10
		Manasamitra	20.5 ± 4.1	21.7 ± 4.2	
7	Albumin (mg/dL)	Brahmi	3.5 ± 0.2	3.7 ± 0.2	0.59
		Manasamitra	3.6 ± 0.3	3.5 ± 1.1	
8	A/G ratio	Brahmi	1.0 ± 0.1	1.1 ± 0.1	0.52
		Manasamitra	1.1 ± 0.1	1.1 ± 0.3	
9	Total Protein (mg/dL)	Brahmi	6.7 ± 0.2	6.8 ± 0.2	0.48
		Manasamitra	6.8 ± 0.2	6.8 ± 0.2	
10	Alkaline Phosphatase (IU/mL)	Brahmi	147.8 ± 27.4	140.0 ± 25.1	0.33
		Manasamitra	140.5 ± 22.9	139.7 ± 19.4	
11	Serum Creatinine (mg/dL)	Brahmi	0.9 ± 0.1	0.9 ± 0.1	0.35
		Manasamitra	0.9 ± 0.1	0.9 ± 0.1	

Expressed in mean and standard deviation.
p values respect to baseline are presented.
ESR- Erythrocyte sedimentation rate, AST-Aspartate aminotransferase, ALT-Alanine transaminase, A/G-Albumin globulin ratio.

impressions, severity reduced from moderate to mild category. CGI-Global improvement showed much improvement. Efficacy index improved to moderate category in *Brahmi vati* and marked category in *Manasamitra vatka* groups. Quality of life improved with both the interventions. Long term follow up and outcomes need to be evaluated as GAD chronicity is associated with Axis I and Axis II co-morbidity. Family relationships, personality disorders and other axis I disorders predict the clinical course of GAD [35].

In the current study *Manasamitra vataka* was considered as control based on a previous publication [20] which reported it's efficacy in patients of GAD with comorbid social phobia. Along with it's wide clinical usage by *Ayurveda* practitioners in the management of anxiety. However there is scarcity of evidences in management of GAD through the *Ayurveda* medicine. *Brahmi vati* had showed leads of anxiolytic action in patients of essential hypertension in our previous study [36] and hence was taken up for the study. *Brahmi vati* has eight ingredients like *Brahmi, Shankhapushpi, Vacha, Krishna Maricha, Gojivha, Swarnamakshika, Rasa sindoora and Jatamamsi* (Supplementary data, Table 4). *Manasamitra vataka* has 73 ingredients, namely *Bala, Nagabala, Bilva, Prisniparni, Shankhapushpi, Vacha, Sweta Chandana, Rakta Chandana, Twak, Pippali, karpura, Rasna, Gojiwha, Padmakeshara, Jivaka, Rushabhaka, haritaki, Bibhitaki, Amalaki, Guduchi, Sariva, Aswagandha, Haridra, Yasthimadhu, Pravala, Mauktika pishti, Loha bhasma etc.* (Supplementary data, Table 5). Brief description of the preparation methods of both the interventions is elaborated along with their respective Tables 4 and 5 Effects of *Brahmi vati* were similar to previously reported findings [36] in which *Brahmi vati* on essential hypertension showed reduction in systolic and diastolic blood pressure, anxiety, sleep onset latency, intermittent awakenings in sleep and improved sleep duration. Action of *Brahmi vati* could be through it's various ingredients. *Brahmi* has antioxidant and stress relieving action, it reduces lipid peroxidation in prefrontal cortex, hippocampus and striatum in rats, aids in recovery of the derangements in neurotransmission and neuronal function and has antidepressant activity [37]. *Shankhpushpi* (*Convolvulus pluricaulis* Choisy) exhibits antidepressant, antistress, neuro regenerative, antiamnesic, antioxidant and immunomodulatory activity [38]. *Jatamamsi* *(Nardostachys jatamansi)* has anxiolytic property and increases brain monoamine and GABA neurotransmitter levels [39]. *Jatamamsi* increased the duration of sleep and improved the initiation of sleep [40] in patients of primary insomnia. *Jatamansi* shows antidepressant effect by inhibiting MAO-A and MAO-B and interaction through GABAergic receptors [41]. *Vacha* (*Acorus calamus* Linn.) produced antidepressant activity through action on adrenergic, dopaminergic, serotonergic, and GABAergic system [42]. *Manasmitra vataka* prevents aluminium-induced neurotoxicity in peripheral and central nervous system of rats [43]. Previous study has shown that *Manasmitra vataka* improved anxiety, depression, sleep, quality of life and global improvement in patients of GAD with comorbid social phobia [20]. *M. vataka* contains various ingredients which have shown effect on anxiety because of its antioxidant, anxiolytic, antistress and adaptogenic properties. A systematic review of human trials on Aswagandha (*W. somnifera*) showed to decrease anxiety and stress [44]. *Amalaki* (Emblica officinalis Garten), one of the ingredient in rasayana ghana vati showed anxiolytic and antidepressant activity [45].

The research design being randomized controlled, double blind with duration of intervention of 45 days are some of the strengths of the study. Comprehensive assessment of anxiety, depression, sleep, disease severity, global improvements and quality of life are the notable components of the study. Use of drugs such as selective serotonin reuptake inhibitors as control would have brought more strength to the study and is a limitation. Study needs to be conducted with a largeer sample and multicentric designs. Interventions carried

for a longer period would have been beneficial. Biological assessments with serum cortisol, electrophysiological assessments like autonomic function tests might have given better insights into drug action.

5. Conclusion

The present study showed that both drugs, Brahmi vati and Manasamitra vataka were comparable in management of GAD. Both drugs appeared to be safe as assessed through serum creatinine levels, liver function test and absence of any adverse drug reactions. *Brahmi vati* has anxiolytic, antidepressant, sleep promoting effect and improves quality of life and decreases blood pressure of pre-hypertensive stages and disease severity. Further studies on Brahmi vati are needed to get better understanding of the drug. *B. vati* can be incorporated into comprehensive treatment strategy of GAD.

Author contributions

B R Tubaki: Conceptualization, Methodology, Writing - Original draft preparation, Writing - Reviewing and Editing, Statistical analysis. Siddhi Khot: Supervision, Data curation, Writing - Reviewing and Editing. Varsha B Gonugade: Visualization, Data collection, Writing - Reviewing and Editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2022.100552.

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