



Research Article

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AN OPEN LABELED, RANDOMIZED, PARALLEL ARMS, CLINICAL TRIAL TO EVALUATE SEDATIVE EFFECT OF LEAVES OF BEEJAPURA (*CITRUS MEDICA* LINN.) AND RHIZOME OF JATAMANSI (*NARDOSTACHYS GRANDIFLORA*) IN ANIDRA (PRIMARY INSOMNIA)

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ABSTRACT

Primary insomnia is a major health issue with a bearing on the morbidity, health related quality of life. Pharmacologic treatment for insomnia has been shown to be associated with significant side effects; hence, it is need to search safe and effective remedies from natural sources. Powder of Beejapura (*Citrus medica* Linn) leaves with honey has been indicated to induce sleep in classical text of Ayurveda. Keeping this in view, open labelled, randomised parallel arm clinical trial was planned to evaluate the efficacy of the leaves powder of *Citrus medica* Linn. on primary insomnia in comparison to Jatamansi (rhizome of *Nardostrachys grandiflora* DC). Patients of primary insomnia belonging to age group of 20-70 years were diagnosed on the basis of diagnostic criteria given for insomnia in DSM – IV-TR. Total 66 patients were registered and randomly allocated in two arms, among them, total 62 completed the trials. Statistically, 30.6% overall effect was provided by Beejapura leaves, whereas 55.6% overall effect was provided by Jatamansi rhizome in the signs and symptoms of Primary insomnia. The difference between both therapies was statistically significant ($p < 0.001$) wherein Jatamansi rhizome produced clinically better result in comparison to Beejapura leaves. Data indicates that Beejapura leaves improved only late sleep induction whereas Jatamansi rhizome provided better improvement in terms of late sleep induction and sleep maintenance.

Keywords: Anidra, primary insomnia, *Beejapura* leaves, *Citrus medica* Linn, Jatamansi rhizome, *Nardostrachys grandiflora* DC

INTRODUCTION

Insomnia is the most prevalent sleep disorder in the general population, and is commonly encountered in medical practices. Chronic insomnia is more prevalent than heart disease, cancer, AIDS, diabetes and several other disorders¹. WHO health survey reveals that about 35 percent of respondents in India have reported mild to extreme difficulty associated with sleeping².

Pharmacologic treatment for insomnia has been shown to be associated with significant side effects, such as residual sedation, cognitive impairment, and psychomotor impairment³. Psychological dependence and rebound insomnia are also risks associated with use of hypnotic compounds.⁴ Hence, it becomes imperative to search out treatment of safe and effective remedies from natural sources which may help patients suffering from insomnia.

In Bhavaprakashsamhita⁵ simple formulation of Beejapura (*Citrus medica*) leaves with honey has been stated to induce sleep. Till date, no research work was conducted to evaluate the efficacy of Beejapura leaves in insomnia. Keeping this in view, clinical study was designed to evaluate the efficacy of Beejapura leaves on primary insomnia. Moreover, Rhizome of Jatamansi (*Nardostrachys grandiflora*) is experimentally as well as clinically proven effective drug for insomnia⁶. Hence, Rhizome powder of Jatamansi was taken as comparator in this clinical study.

MATERIALS AND METHODS

Study design

Open labelled, randomised clinical trial was planned to evaluate the efficacy of the leaf powder of Beejapura (*Citrus medica* Linn.) on insomnia. Jatamansi (rhizome of *Nardostrachys grandiflora* DC) was set as a comparator drug as it was experimentally as well as clinically proved effective drug for insomnia.

Diagnostic, inclusion and exclusion criteria

Patients of primary insomnia (chronic insomnia) were diagnosed by diagnostic criteria given for insomnia in DSM – IV-TR⁷. Patients with secondary insomnia like transient situational insomnia; insomnia associated with neurologic disorders, mental disorders and other medical disorders; drug or alcohol-dependent insomnia; or with systemic uncontrolled disease and out of age group of 20-70 years were excluded from trial. For the purpose of assessing the general condition of the patient and to exclude other pathology the routine haematological and biochemical investigations were carried out before intervention of treatment. Patients fulfilling the inclusion criteria after screening were registered at the OPD of department of Dravyaguna & Kayachikitsa, I.P.G.T. & R.A. Hospital, Jamnagar.

Grouping and posology

Registered patients were randomised in to two groups i.e. group A and group B. In group A, 3 g of powder of Beejapura leaf powder mixed with 5 g honey (Sahapana/vehicle) was administered orally at half hour before bedtime once at night for 4 weeks. While in group B, Jatamansi rhizome powder mixed with 5 g honey was administered with same posology. Total 89 patients were screened, among them, 66 were registered and randomly allocated into group A (n=33) and B (n=33).

Randomization

Randomization sequence was generated with the help of online software accessed through www.randomization.com.

Ethical clearance

Informed consent was taken from all the patients before including them in the trial. Ethics clearance (PGT/7-A/Ethics/2012-2013/3552) and CTRI registration (CTRI/2013/10/004097) was obtained before the commencement of trials.

Evaluation criteria

A detailed proforma was prepared to incorporate demographic data, all signs and symptoms of disease including classical symptoms. Improvement in Anidra (primary insomnia) was assessed on the basis of changes in grade developed for the clinical factors. Chief symptoms were graded from 0 to 3 based on severity and associate symptoms were graded from 0 to 1 based on its presence or absence.

Statistical analysis

Individual effect of drug was calculated by Wilcoxon signed rank test as data generated was paired non-parametric in nature, while Mann-Witney Rank Sum Test were used to compare the effect of both drugs as data generated was unpaired non-parametric in nature.

OBSERVATIONS AND RESULTS

Among 89 patients, 23 were excluded wherein 26% of patients were excluded due to transient situational insomnia, 17% due to insomnia associated with mental disorders 22% insomnia associated with medical disorders and 22% due to systemic uncontrolled diseases. 3 patients were dropped out in group A and 1 in group B (Figure 1). Irregularity in medicine intake and use of concomitant sedative drugs during trial were the reasons for drop out. Average chronicity of disease was recorded as 21 months.

Effect of Beejapura leaves powder (group A)

Beejapura leaf powder with honey for 4 weeks, significantly reduced the major symptoms of insomnia i.e. late sleep induction (58.49%), total sleep duration (30.4%, $p<0.001$) and overall quality of sleep (35.3%, $p<0.001$). The drug did not exhibit significant effect on other two major symptoms such as awakenings during the night ($p=0.06$) and early awakening in the morning ($p=0.25$) (Table 1).

Associated symptoms, like irritability (58%, $p = 0.016$), Shirogourava (headache) (57%, $p = 0.008$), Apakti (indigestion) (68%, $p<0.001$), Angamarda (Body ache) (63%, $p<0.001$) were

also improved significantly. Other associated symptoms like reduced motivation, making errors or having accidents, Tandra (lassitude), Jadya (fatigue), Bhrama (dizziness), and Glani (Nervousness) were not improved by test drug significantly. Test drug did not improve sleep problems interfered with home management, ability to work, social life and close relationships also. (Table 2)

Effect of Jatamansi rhizome powder (group B)

Significant results were observed in all major symptoms such as late sleep induction (69.23%, $p<0.001$), awakenings during the night (76.9%, $p<0.001$), early awakening in the morning (64.71%, $p<0.001$), total sleep duration (66.18%, $p<0.001$) and overall quality of sleep (66.67, $p<0.001$) (Table 1).

Associated symptoms like reduced motivation (53%, $p=0.008$), making errors or having accidents (55%, $p=0.031$), irritability (79%, $p<0.001$), Tandra (lassitude) (59%, $p<0.001$), Jadya (fatigue), (74%, $p<0.001$), Shirogourava (headache) (80%, $p<0.001$), Apakti (indigestion) (64%, $p<0.001$), Angamarda (Bodyache) (81%, $p<0.001$), Jrumbha (Yawning) (71%, $p<0.001$), worry or distress (39%, $p=0.016$) and ability to work (73%, $p<0.001$), were also improved significantly. But drug has not shown improvement in the symptoms of Bhrama, Glani, home management, social life and close relationship problems (Table 2).

Comparison of both arms A and B

In comparison, Jatamansi rhizome powder provided better improvement on patients with problem of late sleep induction ($p=0.035$), night awakening ($p=0.006$) and earlier awakening ($p=0.004$), and it also provided better results on total sleep duration ($p<0.001$) and overall quality of sleep ($p<0.001$) (Table 1, Figure 2 & 3).

In associate symptoms, for Apakti and sleep problems interfered with social life, group A provided 4.8% and 8.3% better relief in comparison with group B. But these differences were not up to a significant level. In comparison with group A, better relief was observed in group B with regard to the symptoms like reduced motivation (10.5%), making errors or having accidents (11.7%), irritability or mood disturbance (20.9%), Tandra (44.5%), Jadya (36.2%), Shirogourava (22.9%), Angamarda (17.6%), Jrumbha (4.8%), Bhrama (33.3%), Glani (10%), worried or distressed about sleep problems (20.1%), sleep problems interfered with home management (42.8%), sleep problems interfered with ability to work (35.8%) and sleep problems interfered with close relationships (16.7%). Difference in the relief of these symptoms between both groups was insignificant. (Table 2, Figure 4, 5 & 6)

Overall effect

Overall effect of therapy is the percentage mean difference between before score and after score of all patients in individual group. The 30.6% overall effect was provided by Beejapura leaves whereas 55.6% overall effect was provided by Jatamansi rhizome. The difference between both therapies was statistically significant ($p<0.001$) indicating Jatamansi rhizome produced clinically better result on symptoms of primary insomnia in comparison to Beejapura leaves (Table 3)

No adverse drug reactions were noted among the patients of both groups.

Table 1: Effect of both drugs on chief symptoms and its comparison

| No | Main Symptoms | Effect in Group A (W) | | Data of Group B (W) | | Comparison between A and B (MW) | | |
|----|--------------------------------------|-----------------------|--------|---------------------|--------|---------------------------------|-----|--------|
| | | Relief in % | SI (P) | Relief in % | SI(P) | Df in % (B-A) | "T" | SI (P) |
| 1 | Late sleep Induction | 58.49 | <0.001 | 69.23 | <0.001 | 10.74 | 690 | 0.035 |
| 2 | Awakenings during the night | 27.27 | 0.063 | 76.9 | <0.001 | 49.63 | 183 | 0.006 |
| 3 | Final awakening earlier than desired | 14.29 | 0.25 | 64.71 | <0.001 | 50.42 | 146 | 0.004 |
| 4 | Total sleep duration | 30.36 | <0.001 | 66.18 | <0.001 | 35.82 | 633 | <0.001 |
| 5 | Overall quality of sleep | 35.29 | <0.001 | 66.67 | <0.001 | 31.38 | 651 | <0.001 |

W: Wilcoxon Signed Rank Test, MW: Mann-Witney Rank Sum Test, SI-Significance, p<0.05 (significant), p <0.01 (highly significant), p<0.001 (highly significant),

Table 2: Effect of both drugs on associated symptoms and its comparison

| No | Main Symptoms | Effect in Group A (W) | | Effect in Group B (W) | | Comparison between A and B ((MW) | | |
|----|--|-----------------------|--------|-----------------------|--------|----------------------------------|-------|--------|
| | | Relief in % | SI(P) | Relief in % | SI(P) | Df in % | "T" | SI (P) |
| 1 | Reduced motivation | 42.86 | 0.25 | 53.33 | 0.008 | 10.47 | 75 | 0.723 |
| 2 | Making errors or having accidents | 42.86 | 0.25 | 54.54 | 0.031 | 11.68 | 62 | 0.715 |
| 3 | Irritability or mood disturbance | 58.33 | 0.016 | 79.17 | <0.001 | 20.84 | 192 | 0.32 |
| 4 | Tandra (lassitude) | 14.29 | 1 | 58.82 | <0.001 | 44.53 | 61 | 0.097 |
| 5 | Jadya (fatigue) | 37.5 | 0.25 | 73.68 | <0.001 | 36.18 | 84.5 | 0.149 |
| 6 | Shirogourava (headache) | 57.14 | 0.008 | 80 | <0.001 | 22.86 | 213 | 0.268 |
| 7 | Apakti(indigestion) | 68.4 | <0.001 | 63.63 | <0.001 | -4.77 | 409 | 0.803 |
| 8 | Angamarda (Bodyache) | 63.15 | <0.001 | 80.77 | <0.001 | 17.62 | 393 | 0.321 |
| 9 | Jrumbha (Yawning) | 66.67 | 0.125 | 71.43 | <0.001 | 4.76 | 61 | 0.901 |
| 10 | Bhrama (dizziness) | 16.67 | 1 | 50 | 0.500 | 33.33 | 26 | 0.476 |
| 11 | Glani (Nervousness) | 40 | 0.750 | 50 | 0.500 | 10 | 21 | 0.905 |
| 12 | worried or distressed about sleep problems | 18.75 | 0.250 | 38.9 | 0.016 | 20.15 | 251 | 0.323 |
| 13 | sleep problems interfered with home management | 0 | 1.00 | 42.86 | 0.250 | 42.86 | 18 | 0.315 |
| 14 | sleep problems interfered with ability to work | 37.5 | 0.250 | 73.33 | <0.001 | 35.83 | 74.5 | 0.173 |
| 15 | sleep problems interfered with social life | 33.33 | 1.00 | 25 | 1.00 | -8.33 | 12 | 0.857 |
| 16 | sleep problems interfered with close relationships | 33.33 | 1.00 | 50 | 0.250 | 16.67 | 13.5 | 0.714 |
| 17 | Disturbed nights/week | 18.62 | <0.001 | 36.32 | <0.001 | 17.7 | 767.5 | 0.013 |
| 18 | Tired or sleepy days/week | 12 | 0.063 | 41.56 | <0.001 | 29.56 | 109.5 | 0.02 |

W: Wilcoxon Signed Rank Test, MW: Mann-Witney Rank Sum Test, SI-Significance, p<0.05 (significant), p <0.01 (highly significant), p<0.001 (highly significant),

Table 3: Total effect of therapies

| Overall effect | | Comparison | |
|----------------|---------|------------|--------|
| Group A | Group B | 'T' | SI (P) |
| 30.6% | 55.6% | 581 | <0.001 |

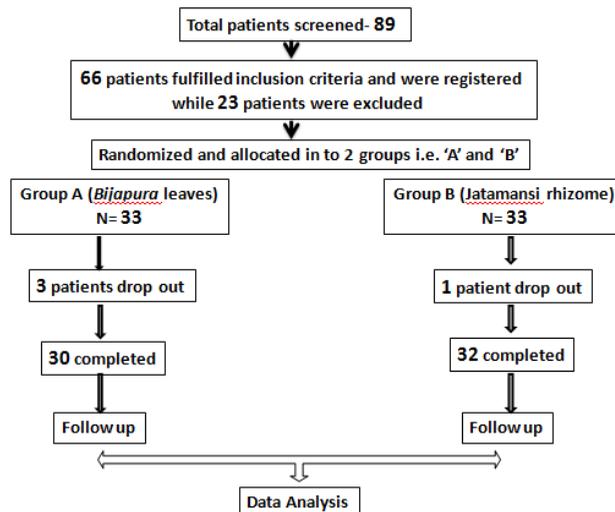


Figure 1: Algorithm of progression of patients in clinical trial

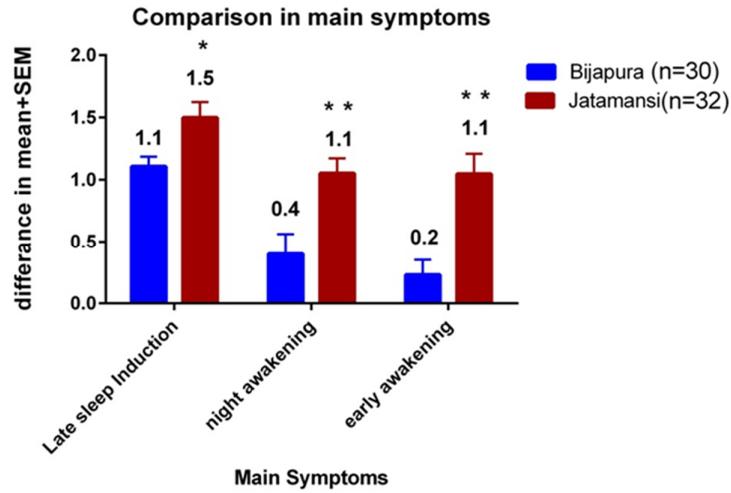


Figure 2: comparison between effects of both arms on main symptoms

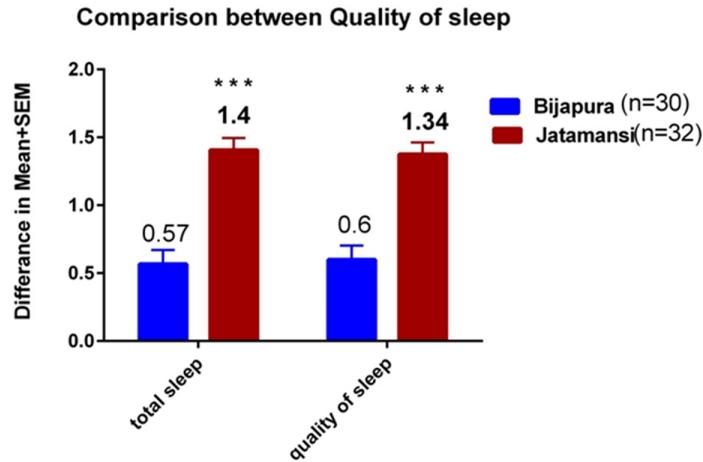


Figure 3: comparison between effects of both arms on main symptoms

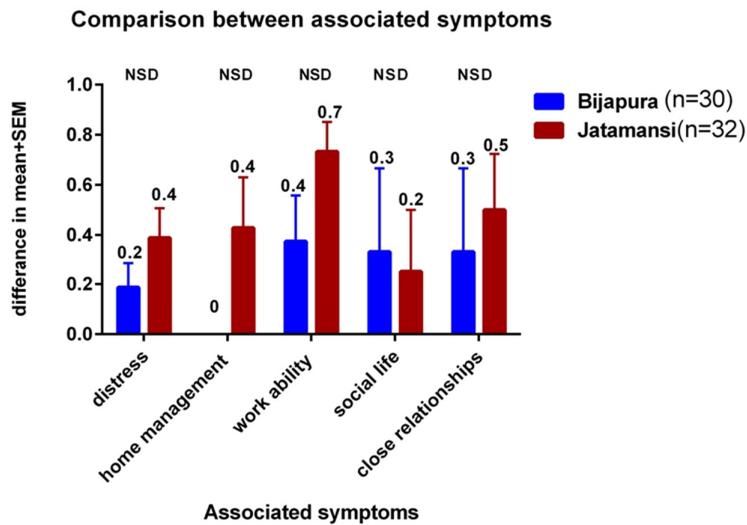


Figure 4: comparison between effects of both arms on associated symptoms

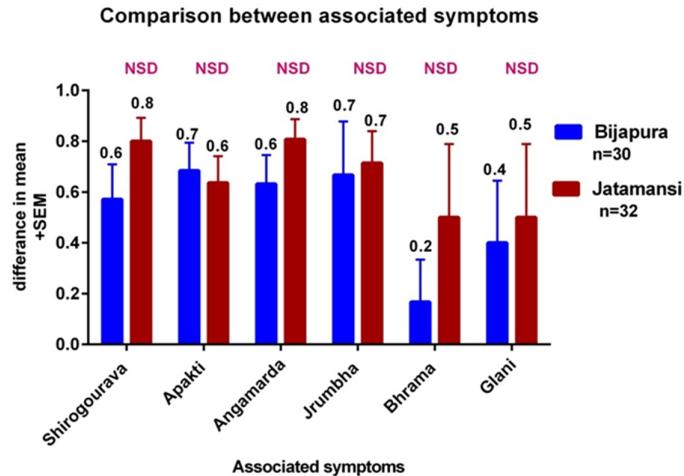


Figure 5: comparison between effects of both arms on associated symptoms

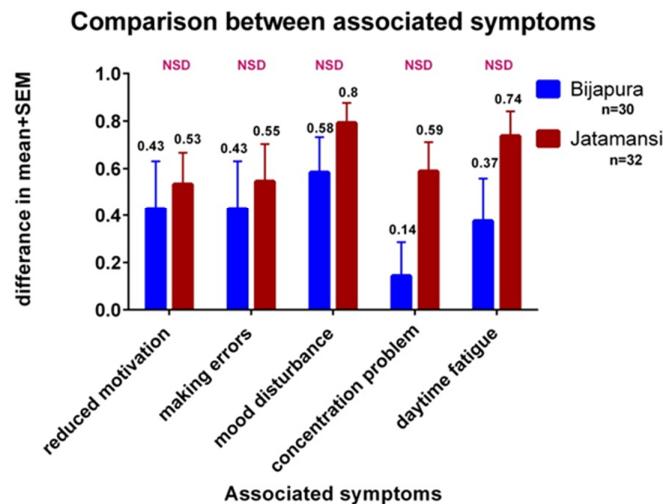


Figure 6: comparison between effects of both arms on associated symptoms

DISCUSSION

Words such as Anidra, Nidranasha and Asvapna are used for insomnia in Ayurvedic literature. Charaka included the Asvapna (Sleeplessness) in 80 Nanatmaja Vataroga (disorders caused by pure Vata factor)⁸. In classical text, symptoms of Anidra mentioned are Jrumbha (yawning), Angamarda (body ache), Tandra (lassitude), Shirogaurava (headache), Jadya (fatigue), Glani (Nervousness), Bhrama (dizziness) and Apakti (Indigestion).⁹ Among these, most of the symptoms can be correlated with symptom of insomnia given by Diagnostic and Statistical manual of Mental disorders IV –Text Revision (DSM IV-TR). It indicates that ancient Acharyas had profound knowledge about physio-pathology of insomnia.

In Bhavaprakashsahita, leaves of Beejapura have been mentioned to treat Anidra wherein it is clearly explained the mode of action of the leaves which induce sleep by relieving Apanavayu (one of the type among five Vatadosha, situated in

colon controls downward movements) vitiation.¹⁰ Beejapura leaves may alleviate Apanavata vitiation leading to proper function of higher centre of brain resulting in the induction and maintenance of proper sleep. Administration of *Madhu* (honey) as vehicle may have increased bio-availability of drugs due to its Chedi (cutting) and Yogavahi (synergistic) properties. Alkaloids and essential oils of the drug might be responsible of sedative and CNS depressant activities of *Citrus medica* leaves by acting on the GABA_A receptor complex.

The result also indicates that Beejapura leaves may be used for early insomnia in which sleep induction is a prominent complaint. This kind of pattern of action of Beejapura may indicate short time bio-availability.

Jatamansi has not been indicated in the management of Anidra (insomnia) in Ayurvedic classical texts, compendia and lexicons, but, Jatamansone (Valeranone), the active ingredient of Jatamansi rhizome, has reported to have sedative and tranquilizing activities by Arora *et al* in 1963.¹¹ Its

administration has a similar behavioural effect to that of benzodiazepine. Jatamansone may enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA_A receptor.¹² Jatamansi also contains alkaloids, Spirojatamol, Valerenic acid, Virolin and is having actions like sedative, hypotensive, anti-inflammatory, anti-stress, CNS depressant, anti-anxiety and analgesic activities.^{13,14} Based on these activities, Jatamansi had provided significant effect on the symptoms of primary insomnia.

CONCLUSION

Clinical study suggested that powder of Beejapura leaves significantly decreased the latency of late sleep induction in patients with primary insomnia, but it was unsuccessful to improve proper sleep maintenance. Associate symptoms like Apakti (indigestion) and Angamarda (bodyache) have responded well to Beejapura leaves. Jatamansi rhizome significantly relieved all the symptoms of primary insomnia clinically in terms of late sleep induction, night awakening, early awakening in morning, total sleep duration and overall quality of sleep. In a nut shell, mild effect (30.58%) was exhibited by Beejapura leaves in comparison to moderate (55.64%) improvement exhibited by Jatamansi rhizome which indicates that Jatamansi rhizome is relatively effective to Beejapura leaves in the management of primary insomnia.

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