کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Efficacy of *Viola odorata* in Treatment of Chronic Insomnia

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Background: Insomnia is the most common sleep disorder that reduces quality of life.

Objectives: Due to side effects of hypnotic drug and the increasing demand for alternative medicine substitutes, violet oil (VO) was used in this study. VO is a known medication in Iranian traditional medicine that induces sleep in insomnia patients.

Patients and Methods: This study was conducted as an experimental pretest-posttest evaluation on VO efficacy in 50 patients with chronic insomnia in Iranian Traditional Medicine Clinic of Mashhad University of Medical Sciences, Mashhad, Iran. Treatment consisted of intranasal drop of VO, two drops containing 66 mg of VO in each nostril nightly before sleeping for one month. All patients were asked to complete an Insomnia Severity Index (ISI) questionnaire before the start of the trial and after one month of treatment.

Results: Improvements in sleep and ISI scores were significantly greater in patients after a month receiving VO drop in comparison with before starting treatment (*P* < 0.05). A few patients reported some complications about VO consumption, most of which were mild and no serious adverse event was encountered.

Conclusions: VO can be presented as a safe, well-tolerated, and effective herbal preparation in patients with chronic insomnia.

Keywords: Violet Oil; Viola Odorata L; Chronic Insomnia; Iranian Traditional Medicine

1. Background

Insomnia is the most prevalent sleep disorder in the general population and it is defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, which results in some form of daytime function impairment (1). It has been shown that almost one-third to one-fourth of the population in industrialized countries report sleep disturbance problems at some point in their lives and approximately 10% have chronic insomnia (2). Insomnia affects many aspects of patient's life; for example, fatigue, day time drowsiness, reduced memory and concentration, depression, anxiety, high sensitivity and irritability, work disturbance, and reduced quality of life are amongst the adverse effects of insomnia (3). To treat insomnia, benzodiazepines are frequently prescribed that increase the probability of adverse effects such as amnesia (4), sedation, slowness, sleepiness, fatigue, headache, irritability, and dizziness (5). Recently, complementary therapies are increasingly used worldwide. When conventional medicine fails to treat chronic diseases efficaciously and without adverse events, many people seek unconventional therapies including herbal medicine (6). Numerous studies in herbal medicine have shown beneficial effects of medicinal plants to treat insomnia (7). Considering patients’ complaints of insomnia and side effects of drug treatments, finding treatments with fewer adverse effects and using complementary treatments becomes more important.

Iranian traditional medicine (ITM) is a traditional medical system based on humoral medicine with a rich literature about insomnia. In ITM, insomnia is called Sahar that is defined as excessive wake that is out of normal range and is considered as a temperamental disease, mainly caused by brain dystemperament (8). ITM scholars believe that the principle of insomnia treatment is correction of brain dystemperament. They mention that insomnia is caused by dryness in brain. According to the theories of humoral medicine, this defect can be resolved by food or drugs with wet temperament. Based on ITM manuscripts, one of the most cited and widely recommended medicinal herbs to treat insomnia is *Viola odorata*.
Violet oil (VO) is derived from sweet violet, *Viola odorata* L., commonly known as sweet violet, belonging to the family Violaceae. It is called Banafshe in Farsi language and is found in the northern areas such as Alamut region (12). In ITM, it has been used to treat insomnia (9-11), cough, fever, common cold, and headache (10). *Viola odorata* contains alkaloid, glycoside, saponins, methyl salicylate, mucilage, and vitamin C (4). Although some studies have recommended *V. odorata* to treat insomnia (4, 11, 12), no certain assessment was found to be concerning its hypnotic effects on humans, except an animal study (13).

2. Objectives
The present study was conducted to evaluate the hypnotic effects and efficacy of VO in patients with chronic insomnia. This is the first study to assess the effect of this herbal drug via nasal route in insomnia.

3. Patients and Methods

3.1. Study Design
This study was an experimental pretest-posttest evaluation that included 50 patients with chronic insomnia. Each subject was visited three times: at baseline, day 15 of follow-up, and at the end of the study. Patients received intranasal VO every night for one month and were followed up for clinical efficacy at day 15 and at the end of four weeks of treatment. A statistician, who was not involved in the study, ensured balanced distribution of sex, age, and insomnia severity index (ISI) score in the group before the study. The study had the approval of the local ethics committee of Shahed University (reference number of 4/158114). Furthermore, the trial was registered in the Iranian Registry of Clinical Trials with registry number: IRCT2012100210991N1. Subjects were given written information and a verbal explanation concerning the study prior to obtaining consent for their participation. All participants signed a written informed consent before recruiting in the study.

3.2. Study Population
The participants were recruited from Iranian Traditional Medicine Clinic of Mashhad University of Medical Sciences, Mashhad, Iran, from January to June 2013. A total of 50 consecutive patients presenting with chronic insomnia were recruited for the study after taking a careful medical history and performing physical examination. Subjects were selected according to our defined inclusion criteria which were willingness to participate, being 16 to 50 years old, and meeting the defined criteria for primary insomnia according to DSM-IV-TR for at least three nights a week in at least six-months period. We limited the age of the sample because the incidence and causes of insomnia are significantly different in younger and older populations, thus requiring unique studies to investigate the effect of VO in these populations. The criteria for primary insomnia according to DSM-IV-TR were as follows: a) The predominant complaint is difficulty in initiating or maintaining sleep or having nonrestorative sleep. b) The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. c) The sleep disturbance does not occur exclusively during the course of another sleep disorder. d) The disturbance does not occur exclusively during the course of another mental disorder. e) The disturbance is not due to the direct physiological effects of a substance or a general medical condition (14).

Our exclusion criteria were being affected by physical diseases such as chronic heart failure, asthma, cancers, and infectious diseases, psychiatric diseases such as major depression, generalized anxiety disorders, psychosis, drug abuse, neurologic diseases such as Parkinson and Alzheimer diseases, other sleep disorders such as sleep apnea, parallel usage of pharmacologic or nonpharmacologic treatment for insomnia, pregnant and lactating women, severe drug allergy, history of severe unusual drug reactions to herbs, and allergic rhinitis. The subjects were not allowed to receive other pharmacologic or non-pharmacologic treatments for insomnia during the study period and all subjects were free to withdraw at any time during the study.

3.3. Preparation of Viola odorata
Dried flowers of *V. odorata* L. were purchased from a local market in Mashhad bazar, the center of Khorasan Razavi Province, Iran, and were identified by Mitra Souzani, the herbalist, and kept at the herbarium of Mashhad school of pharmacy, Mashhad University of Medical Sciences, under the voucher number of 12855. A voucher specimen was preserved in our laboratory for future reference.

3.4. Preparation of Violet Oil
To prepare VO, ITM scholars have used *Amygdalus communis* oil as the basis. For this reason, it is also called almond violet oil. It is believed in ITM that for preservation of quality, prolonged effects, and better penetration in the body tissue, the medicinal herbs should be prepared on the basis of oil (9). To prepare VO, we followed the instructions in ITM textbooks such as Gharabadin Kabir, the largest Persian pharmaceutical manuscript written in 1772 AD by Aghili Khorasani in which 20 chapters on pharmacy and pharmaceutical practice are organized in the first part followed by 28 parts on dosage forms based on active components (10, 11). Therefore, we mixed the violet flowers with sweet almonds in 1:2 proportions and the final VO was obtained under pressure. The obtained oil was puri-
fied and packed in pharmaceutical dark glass containers and each mL (28 drops) contained 924 mg of VO.

3.5. Intervention

Subjects received two drops of VO in each nostril every night before sleep while the weight of each drop was 33 mg. To ensure the compliance of patients, the subjects were asked to return the given box at the end of the month. The box was weighted and the amount of used VO was considered as a measure of drug consumption. Patient who missed more than 20% of total dose of prescribed treatment were considered noncompliant and were excluded from the study.

3.6. Measurements

Medical history was taken and physical examination was performed for all patients and a list of concomitant medications to rule out medical-related or substance-related causes of insomnia was made. Participants also completed a 21-item Beck’s Depression Inventory (BDI) questionnaire (15) to rule out individuals at high-risk for major depressive disorder. In addition, they completed the Berlin questionnaire to rule out individuals at high-risk for sleep apnea (16). Then ISI questionnaires (17) were evaluated at baseline and at the end of one month of treatment. The ISI questionnaire is a short subjective instrument for measuring insomnia symptoms and consequences. The ISI is composed of seven items assessing sleep onset, sleep maintenance, early awakening, interference with daily functioning, perceived prominence of impairment attributed to the sleep problem, concerns about sleep problems, and satisfaction with sleep patterns. Perceived severity of each item is rated on a zero through four scale. A total score ranging from zero to 28 is obtained from summing the seven ratings. This instrument was translated into Farsi language by the investigators and was validated previously in patients with insomnia in Iran (17).

Physical exam and medical history evaluation were performed by a physician. In addition, a urine pregnancy test was performed for women. Finally, the study investigators, a physician and a psychiatrist evaluated all data obtained from the screening visits for study eligibility. The related adverse effects were assessed based on the self-report symptoms, answering a questioning at the end of one month of study, and weekly phone contacts during the 30-day study period. The result showed that at the end of the study, ISI scores had decreased significantly.

3.7. Statistical Analyses

Data was analyzed using SPSS (SPSS Inc, Chicago, IL, USA); the mean, standard deviation, and frequency of variables of interest were obtained as the summary measures. Friedman’s test was used to compare change in variables over the time within the group and the statistical significance was determined at < 0.05.

4. Results

Initially, 66 patients were screened of whom 57 met all eligibility criteria and were included. Four patients refused to participate and three discontinued the intervention at the first week (Figure 1). Then, the results of 50 patients were considered in our analysis. Demographic characteristics of 50 patients are shown in Table 1. There were 36 females and 14 males with chronic insomnia in this analysis, and their mean age was 37.32 ± 9.188 years. For assessment of efficacy, ISI was measured by means of ISI questionnaire at the baseline, at day 15 of treatment, and at the end of treatment. The results are shown in Table 2. ISI score decreased from 16.32 ± 3.755 at the baseline to 12.58 ± 3.592 at day 15 of treatment and to 6.48 ± 4.306 at the end of the study (Figure 2). ISI score had declined significantly during one month of treatment (P < 0.05).

Adverse effects were reported by seven patients. The most common unpleasant reports were postnasal discharge (n = 3), cough (n = 2), and itching/burning sensation in throat (n = 2). All adverse effects were mild and transient. Cough and itching/burning sensation in throat were removed by correcting method of dropping and density of postnasal discharge was decreased and become watery after a few days of taking the drug and then completely resolved. None of this adverse effects resulted to withdrawal from the treatment.

Table 1. Demographic Characteristics of Patients With Chronic Insomnia (n = 50) a, b

| Variable          | Value   |
|-------------------|---------|
| Gender            |         |
| Male              | 14 (28) |
| Female            | 36 (72) |
| Marital Status    |         |
| Single            | 11 (22) |
| Married           | 39 (78) |
| Age, y            | 37.32 ± 9.188 |
| Weight, kg        | 71.76 ± 14.23 |
| BMI, kg/m²        | 26.54 ± 4.808 |
| Occupational Status |     |
| Employed          | 20 (40) |
| Unemployed        | 30 (60) |
| BDI Score         | 11.38 ± 6.809 |

a Abbreviations: BMI, body mass index; and BDI, Beck’s depression inventory.

b Data are presented as No. (%) or Mean ± SD.
Table 2. Effect of Violet Oil on Insomnia Severity Index (n = 50)\textsuperscript{a, b}

| Time Point                      | ISI Score  | Mean Rank | Chi-Square | Df | Sig   |
|--------------------------------|------------|-----------|------------|----|-------|
| Baseline                       | 16.32 ± 3.755 | 2.97      | 98.569     | 2  | 0.000 |
| Day 15 of Treatment            | 12.58 ± 3.592 | 2.03      | 98.569     | 2  | 0.000 |
| End of One Month Treatment     | 6.48 ± 4.306 | 1.00      | 98.569     | 2  | 0.000 |

\textsuperscript{a} Abbreviations: ISI, insomnia severity index; SD, standard deviation; Df, degrees of freedom; and Sig, significance.

\textsuperscript{b} Data are presented as Mean ± SD.

5. Discussion

In the present study, we evaluated hypnotic effects of VO, on patients with chronic insomnia. VO is herbal drugs that is known for its hypnotic and sedative effects in headache (18) and insomnia in ITM (9, 10). Early Persian practitioners believed that insomnia occurs due to brain dystemperament. According to their clinical approach, treatment was correcting the brain dystemperament by herbal medicaments having wet temperament (8, 9). VO with cold and wet nature was considered useful in the management of insomnia (10).

According to the reports of better drug delivery into central nervous system (CNS) through intranasal route in humans or animal models of Alzheimer’s disease and sleep disorders (19), we chose this method of drug administration. Advantages of intranasal drug delivery in allopathic medicine include rapid drug absorption, fast onset of action, fewer adverse effects, self-administration, noninvasiveness, convenient route for long-term therapy, improved bioavailability, avoidance of gastrointestinal tract and the first-pass metabolism and thus, dose reduction in comparison to oral delivery, and potential for direct delivery of drug to the central nervous system via the olfactory region (20). This route of drug delivery has been extensively considered by ITM physicians and has been presented as an important route of drug administration especially for neurologic disorders (9).

In a study on male albino rats, Porecha et al. (21) assessed the efficacy of intranasal consumption of microemulsion of diazepam, lorazepam, and alprazolam for treatment of insomnia and demonstrated rapid and larger volume of selective nose-to-brain transport in rats in comparison with solution and conventional dosage forms (tablets) of benzodiazepines. Moreover, higher lipophilicity of the drug might have favored faster and enhanced uptake of the drug in the brain, facilitating rapid onset and prolonged duration of sleep (21). In this study, oily form of drug was used because ITM scholars believed that preparing drug herbs on the basis of oil makes prolonged effects and better penetration of drug especially when used in the form of intranasal dropping to treat neurologic diseases.

A similar study by Lui et al. to assess intranasal absorption of flurazepam, midazolam, and triazolam in dogs confirmed that these drugs could cross the nasal mucosa.
L. has been reported to be effective in sleep disorders in human beings, an animal study on rats has evaluated sedative and pre-anesthetic effects of V. odorata (27). Even though no study was found that unlike current hypnotic drugs, VO consumption had more effects with lower doses. In addition, it was found that VO can have a significantly positive effect on inducing sleep in patients with chronic insomnia with few adverse effects.

In allopatic medicine, V. odorata L. has been reported to possess sedative (13), anti-inflammatory (23), analgesic (24), antioxidant, and diuretic activities along with other beneficial effects such as antihypertensive, antilipemic, diaphoretic, antipyretic (12), and antifungal activities (25) as well as effects on body-weight reduction (4). Moreover, in gas chromatography-mass spectrometry (GC/MS) analyses, the essential oil of V. odorata L. flowers contains high percentages of monoterpenes and sesquiterpene groups. The dominant components are ty-phenyl butanone, linalool, benzyl alcohol, α-cadinol, globulol, and viridiflorol (25).

As far as we know, no study has been performed on hypnotic effects of this herbal medicinal in human subjects yet. Nevertheless, a study on effectiveness of NSF-3, a fixed dose combination (FDC) of three herb extracts, namely, Valeriana officinalis, Passiflora incarnata, and Humulus lupulus, in alleviating sleep-related problems showed that the effect of this combination is comparable to zolpidem with minimal adverse effects. This study evaluated the impairment of quality of life using ISI and showed statistically significant decline in both groups (NSF-3 vs. zolpidem) without intergroup difference, either at baseline or at the end of study. Duration of this evaluation was 14 days, which was shorter than ours was (26).

Furthermore, a randomized placebo-controlled pilot study showed that chamomile extract could provide mixed benefits on sleep diary measures in comparison to placebo in adults with chronic primary insomnia and found no significant group effects for changes in the ISI (P = 0.44) (27). Even though no study was found on V. odorata effectiveness in sleep disorders in human beings, an animal study on rats has evaluated sedative and pre-anesthetic effects of V. odorata and has revealed that V. odorata extract had better sedation and pre-anesthetic effects than diazepam did but this effect was dose-dependent (13). In addition, linalool is one of the major identified components by GC/MS in the essential oil of V. odorata (25) and it has been proved that linalool composition possesses hypnotic effect via inhalation in animal models (28). In addition, numerous studies have proved that plants containing antioxidant and polyphenolic compounds are neuroprotective (29) and probably these compounds can explain hypnotic effects of V. odorata.

In an in vivo study, hypnotic and CNS-depressant effects of other genera of Violaceae were reported by Ghorbani et al. (30). This study suggested that Viola tricolor extracts would increase sleep duration with no neuronal toxicity and explained that intermediate to low polar agents (such as some flavonoids, sterols, alkanes, and some terpenoids) were responsible for the hypnotic effect of V. tricolor. It has been reported that flavonoids bind with high affinity to benzodiazepine site of the GABA (Gamma-Amino Butyric Acid) receptor and Rutin, a major flavonoid component in V. tricolor, has sedative effects in the brain (30). In another study, monoterpene and sesquiterpene were introduced as the dominant components in essential oil of V. odorata flowers (25), which can explain its hypnotic effects. Moreover, another study reported the presence of melatonin in V. odorata flowers by enzyme-linked immunosorbent assay (ELISA) (31). Melatonin, marketed as a nutritional supplement, has undergone extensive evaluation for its hypnotic properties and circadian-shifting effects (7). Based on the evidence above, we used this herbal drug for insomnia treatment. Unlike most modern medicines where a single known chemical is responsible for all the action of the drug, herbal drugs contain myriad of chemicals. With advancement of analytical techniques, most constituents of these mixtures can be identified but it is difficult to single out the individual constituents responsible for the pharmacologic activity (26). Analysis of fatty acid compositions of VO by GC/MS showed some major component such as oleic acid (70.54%), linoleic acid (18.22%), palmitic acid (8.51%), stea-ric acid (1.58%) and palmitoleic acid (0.69%).

We need to mention some limitations that we had faced in this study. These limitations are mostly common in studies involving human subjects. Firstly, the traditional medicine has two main variables: the first one exists in human subjects, including Mezaj (temperament) and racial/ethnic, sex, age, territory, season, and occupation and the second one is the herbal drugs, which are natural products and their chemical composition and therefore, varies depending on several factors such as geographic source of the plant material, climate in which it is grown, and time of harvest. These variations can result in different bioavailability in humans (29). Secondly, in ITM, particular oil of flowers is not the same as the essential oil of flowers. ITM physicians prepared oil of flowers by two methods including pressing the flower with an oily seed such as almond or sesame and soaking the flower in almond or sesame oil for several months (10). This study used pressing method. Then, another study is needed to compare hypnotic effect of VO and almond oil. Thirdly, sleep evaluation was based only on ISI questionnaire while polysomnography can give more accurate results. Fourthly, our subjects were assessed only for one month and therefore, we could not have any conclusion about long-term efficacy of this compound.

The result of this study showed that VO could have a significantly positive effect on inducing sleep in patients with chronic insomnia with few adverse effects. As it is made in the basis of oil and consumed from nasal route, it has more effects with lower doses. In addition, it was found that unlike current hypnotic drugs, VO consump-
tion does not make the patient resistant to VO and even it acts more effectively a few days after taking the drug. Nonetheless, further studies are highly suggested for evaluation of mechanisms involved in this process. Moreover, it is expected that consuming other hypnotic drugs, which are prepared in the basis of oil and are administered through nasal routes, can be more effective even with lower doses. The current study introduces VO as a potential new drug to treat insomnia.

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کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله