Original Article

Comparative Efficacy of Zolpidem and Nigella Sativa in Treatment of Sleep Disorder and Vasomotor Symptoms in Menopausal Women of Women's General Hospital

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Abstract

Objective: To evaluate the efficacy of Zolpidem and Nigella sativa compared to placebo in treatment of sleep disturbance in healthy postmenopausal women. Menopause is a period that diagnosed after 12 months of amenorrhea and is characterized by a group of symptoms that include irregular menses; vasomotor and urogenital symptoms. The effects of non-hormonal therapies are being widely researched on menopause symptoms. There has been no study to compare Zolpidem and Nigella sativa versus placebo.

Materials and methods: In this double-blind, placebo controlled trial, we compared the effect of Zolpidem with Nigella sativa and placebo in reducing sleep quality in 60 menopausal women. The prior and the later results were compared. We divided the patients into three groups after history taking and physical examination and filling the Pittsburgh questionnaire. Each group received their medication as the following order: Group A: Zolpidem, Group B: Nigella sativa, Group C: placebo. The first group received Zolpidem with the dose of 5 mg for 8 weeks. The second group received Nigella sativa with the dose of 600 mg for 8 weeks. The third group received placebo for 8 weeks. After two months, the Pittsburg questionnaire was filled again.

Results: In the nigella sativa group, we had not significant improvement in sleep quality (p =0.07), hot flashes (p =0.15), palpitation (p =0.56) and night sweets (p =0.08). In zolpidem group, we have seen lack of improvement of hot flashes (p =0.73), and palpitation (p =0.36), which are nonsignificant statistically according to p values, but in zolpidem group, we had significant improvement in sleep quality (p =0.01), and night sweats (p =0.049).

Conclusion: It seems that zolpidem has some effect on improving the quality of sleep in postmenopausal women. zolpidem also is good for night sweats. Nigella sativa was not effective in vasomotor symptoms and sleep quality.

Keywords: Zolpidem; Nigella Sativa; Sleep Disorder; Menopause

Introduction

Today, health systems have drown their most important programs on the base of family health. Women are considered axis of family health, and they are original pattern of education and promotion of

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healthy life to the next generations. However men and women have some shared topics in health issue, but women are faced by special issues due to their physiological conditions. One of these issues is premenopausal period that can cause many problems for women due to low estrogen levels (1).

Menopause is a physiologic event at the end of reproductive period that occur in 40-59 years old and effect on their quality of life. Menopausal period is one of the important stages of human's growth and development, that in spite of its useful and valuable aspects, can due to some problems. This period like the other periods of life have positive aspects such as leaving pregnancy problems, and negative aspects like women's health treating problems and dangers (2).

In this period women are undergoing endocrine, somatic, and mood changes that can take a few years (3).

Based on global statics in the 17th century, only 28% of women reach menopause (4). While today with the advancement of medical sciences can be expect more years to survive for menopaused women, and many of them live until the age of 80 or more, therefore women's health status in the postmenopausal years is more important than before (5).

Postmenopausal years is the important part of life. Women must be enjoy this episode of their life. In this period, most women experience somatic and psychologic symptoms and mood changes. Due to mechanism of creating menopausal symptoms and effect of decreased estrogen level on serotonin and norepinephrine in causing these symptoms, the standard treatment of all of menopausal symptoms is hormone therapy (6). But due to increasing risk of breast cancer and thromboembolic events and proving of no decrease of cardiovascular events while taking estrogen, non-hormonal remedies for menopausal symptoms is taken into consideration.

Sleep disorders are one of most important and common symptoms of menopausal period, and they are very effective on quality of life.

Despite the importance of these symptoms and their important effect on quality of life, little studies have been done on it. The most suggestive treatment for these sleep disorders, contain SSRI and SNRI drugs.

But due to complications of these drugs, many studies have been done to evaluate other drugs and effective herbals. In Davari-Tanha, et al study citalopram and venlafaxine are equally more effective than placebo in reducing sleep disturbance and severity of hot flashes, while citalopram is more effective in reducing frequency of hot flashes than venlafaxine. Meanwhile, venlafaxine is more effective than citalopram (7). In treatment of depression in postmenopausal women.

Zolpidem is a non-benzodiazepine sedative drug that acts with specific attachment to omega type of GABA receptors in the brain. This drug has sedative, muscle relaxant, weakly anti-epileptic effects. It can cause increasing short wave sleeping, but no changes in second part of sleeping, and it's useful for starting sleep in these patients.

Peak plasma concentration of drug is in 1 to 2 hours after oral consumption. Its metabolism is usually by Cyp3a4 and Cyp2c9 enzymes. Half-life of this drug is 2-3 hours and its clearance is by urine (48-67%) and gastrointestinal (42.29%). Zolpidem is in forms of 5 and 10 mg tablets. The starting dose of zolpidem is 5 mg before bedtime (8). It seems that zolpidem is a good option for treatment of sleep disorder in these patients.

The other non-hormonal remedies are herbals. Herbals were the main resource of treating human's illness and traditional medicine always has this potential to offer a new drug. The importance of the most of these drugs is known for scientific community (9).

The most common medical treatment to reduce the symptoms of menopause is hormone replacement therapy (HRT) (10). Resent evidence suggests that HRT increases the risk of breast cancer and cardiac attacks (11). Therefore, because of unwanted side effects of HRT, that occur in the long term, most women have switched to complementary and alternative therapies, hopping that these therapies will eliminate menopausal symptoms (12-13-14). Approximately 4% of women treat their menopausal symptoms with these methods (15).

Since 1980, WHO has encouraged countries to identify and operate of alternative medicine. In this field, Nigella sativa is one of these plants. It is a beautiful and small yearly plant that has many uses as a medical plant in the Islamic medicine, Greek medicine, and Indian medicine (9). Nigella sativa has small flat beads with regular bumps of 1-3 mm. It has a slightly scented smell and bitter taste (16).

Thymoquinone is the effective substance of Nigella sativa (17). Studies on Nigella sativa have proven that this plant has an active therapeutic component, and traditional uses of it confirm that. Because of various biological activity of Nigella sativa, it is effective on various diseases such as diabetes, rheumatoid arthritis, osteoporosis, hypercholesterolemia, hypertension,

inflammatory diseases, diseases of gastrointestinal system and skin diseases. The mechanisms of these beneficial effects are not clearly known, but antioxidant and anti-inflammatory effects and its immune system modification and angiogenesis effects may play a role (18). Extensive use of herbal therapeutic products among women reveals the need for research in these interventions. Previous studies have been less studied the effects of zolpidem and nigella sativa on improving sleep quality in postmenopausal women. In Dorsey and et al study at 2004, zolpidem has been effective in improving sleep disorders in postmenopausal women (19).

Therefore, the benefits of Nigella sativa in treating menopausal symptoms should be evaluated.

This study is a randomized prospective double-blind placebo-controlled trial. The participants were the patients who referred to menopausal clinic of tertiary university based hospital.

Materials and methods

Sixty menopausal women who referred to menopausal clinic of tertiary university based hospital with the complaint of sleep disorder were enrolled to the study (Figure 1). Our randomization method in this study was block randomization.

The ethics committee of Tehran University of Medical Sciences approved the study protocol (Trial registration Iranian Registry of Clinical Trials 201306192576N7). All of the collected data were stored and treated according to the ethical guidelines of medical research. All patients were given an informed consent about the aims and procedures and voluntarily. The data file was anonymous, and the identity of participants was protected. Those who have a history of antidepressant or benzodiazepine usage were excluded from the study.

At the first visit, after taking history and physical examination and getting patient's written consent, from the Pittsburgh questionnaire filled by them. Sleep disorder's Pittsburgh questionnaire checks the sleep disorders by 7 items. Maximum score of it is 21. Those patients whose rating is more than 5, have some degrees of sleep disorders, and quality of their sleeping is considered poor. This questionnaire dose not categorize the severity of sleep disorders.

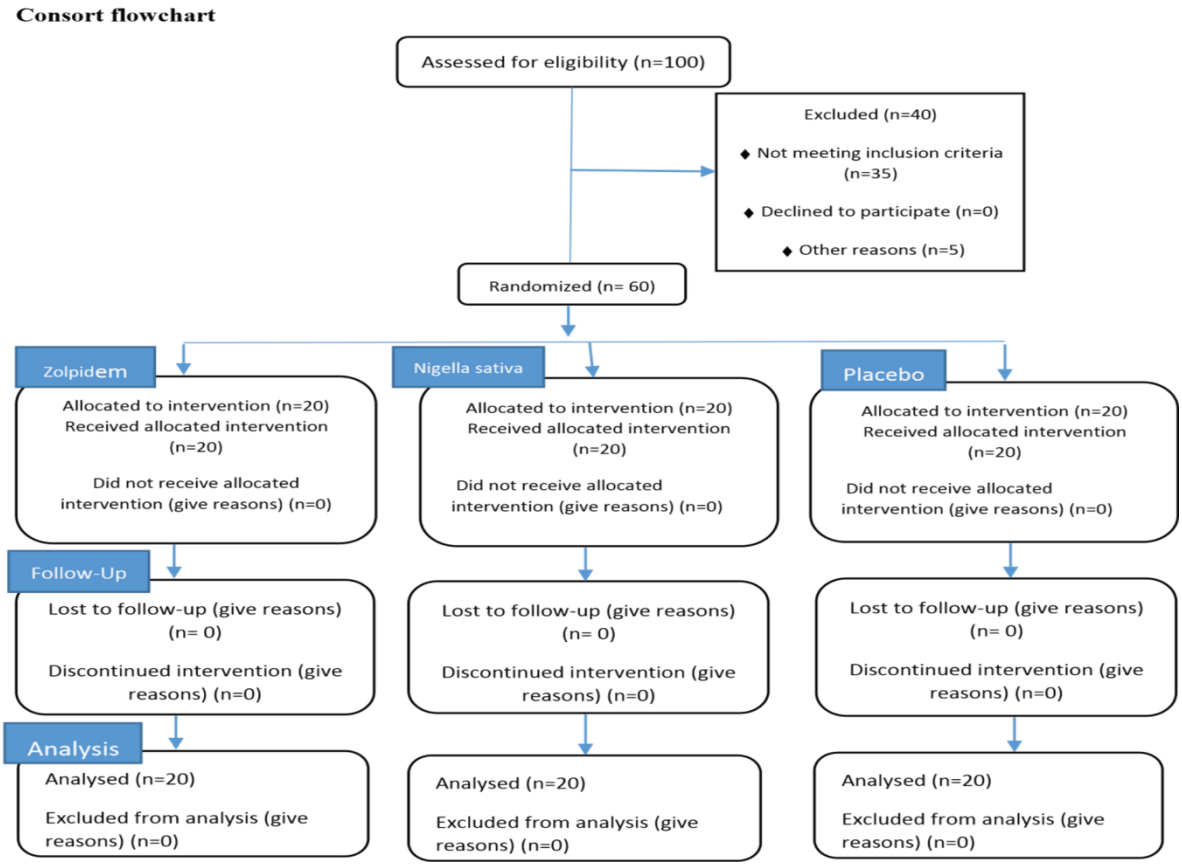

Figure 1: consort flow chart of patients

We divided the patients into three groups after history taking and physical examination and filling the Pittsburgh questionnaire. Each group received their medication as below: Group A: Zolpidem (5 mg daily at bedtime, Sobhan factory), Group B: Nigella sativa (1 mg daily, Iranian factory), Group C: placebo. The first group received Zolpidem with the dose of 5 mg for 8 weeks. The second group received Nigella sativa with the dose of 600 mg for 8 weeks. The third group received placebo for 8 weeks.

At the first, extraction of 30 gr Nigella sativa were done by using Soxlet-extaracor (Manufacture co., MERCK), then it passed from filter paper and condensed at 50 C by distiller and oily extract of it in yellow color and volume of 5.3 ml obtained. In the next step in order to supply essential oil, oily extract added to distilled water and essential oil prepared by using Clevenger apparatus.

Because of the small amount of essential oil (0.3 ml), 0.7 ml hexane added to it for isolating. Then it dried with anhydride sodium sulfate and stored at 4 C for preparation of gas spectrograph/mass spectrometry. This extract was yellow with a bitter taste.

Analyses showed that there are 0.065 gr thymoquinone per 5.3 gr extracted oil. 5.3 ml of thymoquinone and 5.3 gr of it is equivalent. The using dose of thymoquinone in patients are 0.6 mg per kg of body weight. So in this study the using dose extracted oil in human 0.05 ml/kg of body weight was considered. This amount of dose was absolutely safe.

Medications were packaged in matched packages to prevent the patient or the distributor from knowing the contents until the opening of the envelope. 8 weeks later, the Pittsburg questionnaire was filled again.

Data analyzed by SPSS 16 software. In this step results form 2 drugs and placebo were compared whether these drugs had an improvement of sleep disorders relative to placebo or not.

Results

The average age of a total of 60 participating patients was 53.6 ± 4.247 years old. In this study, minimum age in the control group, Nigella sativa group and zolpidem group were respectively 43-59, 49-64, 48-62. The mean menopause age of participants was 48.65±4.305. The range of parity was 0 to 5 and mean was 2.98 ± 1.081. The participant's job was as bellow: House-wife: 76.7%, teacher: 10%, nurse: 8.3%, employee: 3.3% and physician: 1.7%.

The average score of PSQI questionnaire in placebo group was 11 before, and 9.5 after intervention, and in zolpidem group and Nigella sativa group was respectively 5.65 before and 4.9 after intervention in zolpidem group and 7.2 before and 6.0 after intervention in Nigella sativa group (p =0.45).

Quality of sleeping and vasomotor symptoms and night sweets and palpitation of participants before and after intervention are shown in table 1.

Table 1: Comparison between sleep quality and vasomotor symptoms before and after intervention

	Before		After		p-value*
	Good	Poor	Good	Poor	
Sleep quality					
Placebo	3	17	3	17	1
Nigella sativa	7	13	8	12	0.07
Zolpidem	10	10	12	8	0.01
Hot flashes					
Placebo	20	0	18	2	0.15
Nigella sativa	18	2	16	4	0.15
Zolpidem	7	13	8	12	0.73
Night sweats					
Placebo	17	3	15	5	0.15
Nigella sativa	17	3	14	6	0.08
Zolpidem	7	13	13	7	0.049
Palpitation					
Placebo	13	7	14	6	0.31
Nigella sativa	12	8	11	9	0.56
Zolpidem	7	13	10	10	0.36

*p-value for comparing before and after intervention according to Mac-Nemar test

The main index measured in this study, was sleep quality index (PSQI). The mean scores obtained from analysis of the PSQI questionnaire in 3 groups were compared before and after intervention (table 2) (p = 0.45).

Table 2: The mean score (± SD) of PSQI questionnaire before and after intervention

Case or control	Before	After	Mean difference	p-value*
Placebo	11 ± 5.3	9.5 ± 3.8	-1.5	0.45
Nigella sativa	7.2 ± 3.3	6.6 ± 3.6	0.6	
Zolpidem	5.65 ± 4.3	4.9 ± 1.9	-0.75	

According to the standard questionnaire PSQI, values above 5 mean poor sleep quality. Accordingly, the status of sleep quality of patients in the three groups before intervention is as follows: In control group, 3 people had good sleep quality and 17 people had poor sleep quality. In nigella sativa group, 7 people had good sleep quality and 13 people had poor sleep quality. In zolpidem group, 10 people had good sleep quality and 10 people had poor sleep quality.

Quality of patient's sleep after intervention in all 3 groups is as follows: In placebo group, 3 people had good sleep quality and 17 people had poor sleep quality. There was no statistically significant difference between before and after treatment by placebo in sleep quality (p = 1)

In nigella sativa group, 8 people had good sleep quality and 12 people had poor sleep quality. There was no statistically significant difference between before and after treatment by nigella sativa in sleep quality (p =0.07)

In zolpidem group, 12 people had good sleep quality and 8 people had poor sleep quality. There was no statistically significant difference between before and after treatment by zolpidem in sleep quality (p =0.01)

In present study, along with the standard PSQI questionnaire, patients were asked about vasomotor symptoms before and after intervention to assess the effects of zolpidem and nigella sativa on the resolution of these symptoms, which are as follows:

In the placebo group, we had not significant improvement in sleep quality (p =1), hot flashes (p =0.15), palpitation (p =0.31) and night sweets (p =0.15).

In the nigella sativa group, we had not significant improvement in sleep quality (p =0.07), hot flashes (p =0.15), palpitation (p =0.56) and night sweets (p =0.08).

In zolpidem group, we have seen lack of improvement of hot flashes (p =0.73), and palpitation (p =0.36), which are nonsignificant statistically according to p values, but in zolpidem group, we had significant improvement in sleep quality (p =0.01), and night sweats (p =0.049) There were no complications such as nausea, vomiting, headache and constipation in our study group.

Discussion

Nigella sativa with zolpidem were used in this study and their effect on improving the quality of sleep hot flashes, night sweets, palpitation in postmenopausal women were evaluated. In this study, 60 participants were enrolled in the study. Twenty participants were enrolled in the control group, 20 participants were in the Nigella sativa, and 20 participants were in the zolpidem group. All three groups were demographically at the same level and were comparable. Mean age at control group, nigella sativa group, and zolpidem group the same. The role of the age in various forms has also reported in many studies. The Kravitz's study in 2003, rejects the relationship between age and sleep disorders (20). On the contrary, the study of Timur et al. suggests that every year increasing of age is equivalent to 5 percent increase in risk of sleep disorders (21).

The main index measured in this study, was sleep quality index (PSQI). The mean scores obtained from the analysis of the PSQI questionnaire in 3 groups were compared before and after intervention. (p = 0.45). This means that the observed changes are not statistically significant.

As mentioned above, PSQI questionnaire had no significant difference before the intervention in the 3 groups, and groups did not differ from the baseline. But after the intervention, according to PSQI questionnaire, patient's sleep quality in both zolpidem and nigella sativa groups were improved. These findings were statistically significant only in the zolpidem group.

Improving sleep quality of postmenopausal women has been less studied in previous studies. In Dorsey et al. study at 2004 zolpidem has been effective in improving the quality of sleep in postmenopausal women (19). Our study also has the same result.

Finally, analysis of our data from PSQI questionnaire showed that zolpidem, are effective on improving the quality of sleep in postmenopausal women. Zolpidem also had a good effect on night sweats. Nigella sativa was not effective in vasomotor symptoms and sleep quality.

Study in longer periods with larger sample sizes can achieve the results of drugs and their related complications with higher accuracy and reliability. Using multi centers instead of one center can add value of the results, which is done by increasing the sample size as well as more variance and dispersion of patient's characteristics such as biological, ethnic, environmental and other characteristics. In this study only presence or absence of symptoms was checked, which is suggested that further studies be conducted to compare the severity of the symptoms.

Conclusion

In this study, after the intervention, according to PSQI questionnaire, patient's sleep quality in zolpidem group were improved. As well, analysis of our data showed that zolpidem are effective on night sweats. The effect of Nigella sativa in vasomotor symptoms and sleep quality was not statistically significant.

Conflict of Interests

Authors have no conflict of interests.

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