ORIGINAL ARTICLE

THE ROLE OF PAROXETINE IN POST-MENOPAUSAL HOT-FLASHES FREQUENCY REDUCTION

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ABSTRACT

Background: To evaluate the effects and safety profile of Paroxetine on hot – flashes in post – menopausal women.

Methods: It was prospective open label control clinical trial. This study is conducted in the Department of pharmacology & Therapeutics in collaboration with the Department of Obstetrics & Gynecology JPMC. The patients were selected from outpatients department (OPD) of Obstetrics & Gynecology. Duration of the study was 12 month from January 2014 to January 2015. Enrolling 180 outpatients who had menopause with hot flushes divided into three groups. The Greene Climacteric Score Scaling was applied to observe the effects of 12.5mg, 20mg Paroxetine on frequency of hot flashes as compared to Placebo.

Results: Mean GCS scoring frequency in 12.5mg Paroxetine group at 12 week was 1.97±0.31 and the baseline 2.64±0.29. In 20mg Paroxetine mean GCS at baseline was 2.76±0.23 and 12 week 2.04±0.12. Where as in Placebo mean GCS scoring frequency at 12 week was 2.80±0.24 and at baseline 2.76±0.24.

Conclusion: The frequency of hot flashes with Paroxetine 20mg and 12.5mg, is significantly reduced in post menopauseal women as compared to Placebo.

KEYWORDS: Menopause, Hot flashes, Greene Climacteric Scale, Paroxetine

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INTRODUCTION

Menopause is defined as ceasing of menstruation. Between 45 – 50 years is the mean age of women when menstruation is stop. Menopause is opposite of word Menarche means start of menses.[2] Medically menopause occurs when a woman has no vaginal bleeding for a year or it also defined as decrease production of hormones by ovaries that are estrogen or progesterone.[1] It occurs early in women who smoke tobacco and who have removed uterus and ovaries by surgery. Chemotherapy can also cause early menopause. [3]

In the Western world, the typical age of menopause (last period from natural causes) is between 40 and 61 and the average age for last period is 51 years. The average age of natural menopause in Australia is 51.7 years. In India and Philippines, the median age of natural menopause is considerably earlier, at 44 years.[4] The classic symptom being the hot flush. Women in the United States report more hot flushes than women from developing countries. [6]

Hot flashes, a common symptom of menopause and perimenopause, are typically experienced as a feeling of extreme heat with sweating and rapid heartbeat and may typically last from two to thirty minutes for each incidence, ending just as rapidly as they began. The sensation of heat usually begins in the face or chest, although it may appear in

different areas such as the back of the neck, and it can spread all over the whole body. Due to this internal sensation, the surface of the skin, especially on the face, becomes hot on touch. This is the origin of the alternative term "hot flush", since the sensation of heat is often go together with by visible reddening of the face. Excessive flushing can lead to rosacea.[5]

Menopause occurs due to the natural or surgical cessation of estradiol and progesterone production by ovaries, the hormones which make reproduction possible and influence sexual behavior. After menopause, estrogen continues to be produced in other tissues, such as bone, blood vessels skin and even in the brain. However, some hormonal level decreases very slowly like of total and free testosterone, as well as dehydroepiandrosteron sulfate (DHEAS) and androstenedione & androgen level.[6]

In the United States more than 25 million post-menopausal women affected by hot flushes per year in which 4 million women reported severs symptoms [8]. In the Western world, the typical age of menopause (last period from natural causes) is between 40 and 61 and the average age for last period is 51 years. The average age of natural menopause in Australia is 51.7 years. In India and the Philippines, the median age of natural menopause is considerably earlier, at 44 years[5].

The stages of the menopause changes, according to follicle-stimulating hormone (FSH) levels released by pituitary. During the normal menstrual cycle the ovaries produce estradiol, testosterone & progesterone in a cyclical pattern under the control of FSH & LH, release by Pituitary hormone. Up to the menopause the estradiol level may relatively increase or unchanged because of the FSH level[6].

During the pre-menopausal, menstrual patterns can show shorter cycling (by 2–7 days) or longer cycles remain possible. There may also be irregular bleeding (lighter, heavier, and spotting). Dysfunctional uterine bleeding is often experienced by women approaching menopause due to the hormonal changes that accompany the menopause transition. In post-menopausal women, any genital bleeding is an alarming symptom that requires an appropriate study to rule out the possibility of malignant diseases. However, spotting or bleeding may simply be related to vaginal atrophy, a benign sore (polyp or lesion) or may be a functional endometrial response. The European Menopause and andropause Society have released guidelines for assessment of the endometrium, which is usually the main source of spotting or bleeding[10].

Before menopause, amount of flow during menses become irregular, sometime longer than usual or shorter, or may be light or heavy. At this time some women may experience hot flashes, which occur in the form of sweating, shivering, and reddening of skin, vaginal dryness, sleep disturbances and mood changes. Which decrease or stop after a year or more than two years. Symptoms may vary between two women [14]. Premature ovarian failure (POF) is diagnosed or confirmed by high blood level of follicle stimulating hormone (FSH) and luteinizing hormone (LH) on at least 3 occasions at least 4 weeks apart. Other causes of premature ovarian failure include autoimmune disorders, thyroid disease, diabetes mellitus, chemotherapy, being a carrier of the fragile X syndrome gene, and radiotherapy. Some of spontaneous cases of premature ovarian failure is unknown and is generally idiopathic[15].

Menopause is natural, physiological & aging process with consequences of almost all the oocytes & ovarian follicles in the ovaries leading to increase in circulating follicle stimulating hormone (FSH) & (LH) level because of decrease no of oocytes & follicles leading to decrease estrogen. This decrease in the production of estrogen leads to the premenopausal symptoms of hot flashes, insomnia and mood changes. Long-term effects may include osteoporosis and vaginal atrophy. Continuous possible risk of atherosclerosis, osteopenia and osteoporosis [17].

Women who have some sort of functional disorder affecting the reproductive system (e.g., endometriosis, polycystic ovary syndrome, cancer of the reproductive organs) can go into menopause at a younger age than the normal timeframe. The functional disorders often significantly speed up the menopausal process. An early menopause can be occur because of cigarette smoking, higher body mass index, joking, hypertension, increased blood lipids and body weight [19]. Studies show that hot flushes & other vasomotor symptoms are most prevalent in different countries. This prevalence of hot flushes may differ in different women, according to altered factors including lifestyle, climate, and women role & aging process[20].

Hot flushes pattern changes in different women may vary & affect the stages of menopause [21]. Other physical symptoms of menopause include: lack of energy, joint soreness, stiffness, back pain, breast enlargement, breast pain, heart palpitations, headache, dizziness, dry, itchy skin, thinning, tingling skin, weight gain, urinary incontinence, urinary urgency, interrupted sleeping patterns, heavy night sweats, hot flashes. A diagnosis of menopause can be done by measuring hormone levels in both blood and urine. Treatment of symptoms of menopause with respect to hot flashes, advice to avoiding smoking, caffeine, and alcohol is often advice. Sleeping in a cool room[22]. Menopausal hormone therapy (MHT), clonidine, gabapentin, or selective serotonin reuptake inhibitors are treatment of choices. Exercise may help with sleeping problems. MHT is

usually associated with some severe side effects. Serotonin reuptake inhibitors now FDA approved for menopausal hot flashes[24].

METHODS

In 12–week enrolling 180 outpatients who had menopause with hot flushes divided into three groups. The Greene Climacteric Score Scaling was applied to observe the effects of 12.5mg, 20mg Paroxetine on frequency of hot flashes as compared to Placebo. Post-menopausal women with hot flushes of 40-65 years of age. Criteria for menopause, FSH 40 ml IU/ml. Estradiol ‹ 20pg/ml (69.34pmol/l).14 bother some hot flashes/week. Amenorrhea for last 12 consecutive months are included in this study. Active cancer, any chronic cardiac, hepatic & renal disease. Patients on chemotherapy or radiotherapy. Previous history of allergy to study drugs are not included in this study. Clinical parameters. Liver function test, Electrocardiography, Urea & creatinine, Follicle stimulating hormone (FSH), Estradiol level. Greene Climacteric Scale scoring (GCS) performed during the study.

Multivariate generalized linear model was used to compare the mean Greene climacteric scale scores, among three study groups (A to C) at each level independently (baseline ,4th, 8th and 12th week), results of multiple comparison under the LSD test were also reported, p-values less than 0.05 were considered significant.

RESULTS

A total no of 180 post-menopausal patients with of hot flashes were enrolled, 60 patients received 12.5mg Paroxetine, another 60 patients received 20mg of tab Paroxetine and third group 60 patients received Placebo.

Table 1: COMPARISON OF MEAN GREENE CLIMECTERIC SCALE AMONG STUDY GROUPS

Follow-up	A= Placebo (n=60) Mean ± S.D	B= 12.5 mg (n=60) Mean ± S.D	C= 20 mg (n=60) Mean ± S.D	p-value	Multiple Comparison Between Groups		
					p-value A vs. B	p-value A vs. C	p-value B Vs. C
Baseline	2.76 ± 0.24	2.64 ± 0.29	2.76 ± 0.23	0.02	0.02*	0.86	0.013*
4th Week	2.75 ±0.24	2.45 ± 0.27	2.54 ± 0.28	0.00	<0.01*	<0.01*	0.06
8th Week	2.71 ± 0.27	2.27 ± 0.31	2.30 ± 0.28	0.00	<0.01*	<0.01*	0.94
12th Week	2.80 ± 0.27	1.97 ± 0.31	2.04 ± 0.12	0.00	<0.01*	<0.01*	0.17

***P<0.05 was considered significant using LSD**

There was a significant mean difference observed in Greene Climecteric Scale scores at baseline, 4th week, 8th week and 12th week with p-value less than 0.05. Results of multiple comparison under the LSD test showed that, at baseline, there was significant mean difference observed between placebo versus 12.5 mg group and 12.5 mg group versus 20 mg group with p-value 0.02 and 0.013 respectively, however at baseline the differences between placebo and 20 mg group were found statistically insignificant, with p=0.86, further at 4th, 8th and 12th week, the mean differences were not statistically significant for 12.5 mg group and 20 mg group with p-values more than 0.05, however placebo gives significant mean differences with 12.5 mg group and 20 mg group with p-value <0.01.

DISCUSSION

Due to advancement in treatment of hot flushes of menopause, and after approved of SSRI, antidepressant drug for the treatment of hot flushes by Food and Drug Administration in July 2013, the management is continuously evolving.[19]

This non-hormonal treatment for vasomotor symptoms associated with menopause, a therapy containing the selective serotonin reuptake inhibitor (SSRI) Paroxetine mesylate is a good addition in gynecologist's dictionary.[20]

Large clinical studies have demonstrated role of Paroxetine in the reducing frequency of hot flushes in menopausal women such as randomized, place-

bo-controlled, 26-week trials in the United States of America compared with placebo demonstrated the role of Paroxetine at dosages of 12.5 mg per day & 20 mg per day was associated with significantly reduced mean monthly hot flashes frequency after the first month of treatment ($p<0.001$)[12]. We also compare the placebo with Paroxetine 12.5mg and 20mg per day dosage to see the efficiencies of the drug associated with significantly reduced mean monthly hot flushes frequency. The results of the present clinical trial proved the effectiveness of the different dosage of Paroxetine as compared with placebo[14].

When we compared tab Paroxetine 12.5mg/day group A with 20mg/day group B statistically there was considerably progress in mean hot flushes frequency in group A from baseline to 12 week which was 2.64-1.97 (2.42%) decrease and in group B 2.76-1.04 (3.8%) decrease in mean Greene Climacteric Score as compared to placebo15. Randomized, double-blind, placebo-controlled, 12 week, clinical trial, conducted by Clement et al., 2011 was also in accordance with our study observed the effectiveness of Paroxetine 12.5 mg/day was associated with a highly decreased in mean hot flashes frequency which remain sustained[16,17].

A randomized, double-blind, placebo-controlled, 12 week hot flashes trials, Paroxetine 12.5 mg/day was connected with a decrease in mean hot flashes occurrence which remain persistent. It is suggested for most patients with hot flashes &analyzed its safety & acceptability of drug.In which the most common adverse events in paroxetine treated patients were paresthesia (50.5%), fatigue (15.0%), anorexia (14.5%), upper respiratory infection (14.0%), cognitive impairment (13.7%), nausea (13.2%), diarrhea (11.1%) & decrease weight (9.1%), these adverse events were mild to moderate in severity [24].

CONCLUSION

It was found that the frequency of hot flashes in post-menopausal women was highly significantly reduced by treatment with Paroxetine 20mg and 12.5mg, as compared to Placebo. But the 20mg Paroxetine was more effective as compared to 12.5mg Paroxetine. The drug may be alternate therapy to hormonal replacement therapy with good compliance and efficacy.

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