The effect of different dosage of pipecline on hot flushes in postmenopausal woman of Jahrom, Iran.

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Abstract

Introduction: Menopause is one of the natural stages of women’s life usually begins in 45-55 y old. The most common symptom is hot flushes. The aim of this study is to evaluate the effect of different doses of pipecline on hot flashes of post-menopausal women.

Method: 69 postmenopausal women referred to Dr. Rasekh clinic was entered to the study and were randomly divided into 3 groups, first group; 300 mg pipecline daily, second group; 300 mg pipecline twice a day and third group; hormone replacement therapy (1.25 mg conjugated estrogen for 25 d and 10 mg dydrogesterone for 15 d). Hot flushing symptoms were evaluated before and after intervention using Blatt-Kupperman Menopausal Index (BKMI). The data were analysed by SPSS 21 software.

Result: BKMI had a reduction of 17.91 in first group, 20.9 in second group and 20.96 in third group.

Conclusion: We found that a higher dosage of pipecline leads to a significant reduction in hot flushes rate and according to the effectiveness and also lack of side effects related to the higher dose of pipecline, it seems to be an appropriate alternative for hormone replacement therapy to treat the menopausal symptoms in high dosage.

Keywords: Hot flash, Menopause, Piascledine, Phytoestrogen. Abbreviations: HRT: Hormone Replacement Therapy; HR: Hormone Therapy; SSRI: Selective Serotonin Reuptake Inhibitors; CHD: Coronary Heart Disease.
The patients were selected through convenience sampling and randomly divided into three groups. According to the previous researches, considering CI=95% and power=80% the sample size in each group was determined 23, so the total sample size was 69.

**Study participants**

All the menopause women with hot flashes who referred to the Dr. Rasekh clinic whose diagnosis was confirmed by the Kupperman index were entered to the study. We regarded them as the menopause ones if they didn’t experience any menstrual flow for a minimum of 12 months.

**Inclusion criteria**

The patients who had not used hormone therapy (except first group), dietary supplements and herbal medicines to relieve menopausal symptoms were entered to the study.

**Exclusion criteria**

The women who were not able to use or continue their drugs due gastrointestinal symptoms were excluded.

**Intervention**

The patients were randomly divided into three groups. The first group received 300 mg piascledine once a day for 3 months. The second group received 300 mg piascledine twice a day for 3 months and the third group received HRT (1.25 mg conjugated estrogen daily for 25 d and 10 mg dydrogestrone daily for 15 d). All three groups were evaluated 4 times based on the Kupperman Index: before the intervention, 1, 2 and 3 month after that.

**Questions**

The Kupperman index is a numerical conversion index including 11 menopausal symptoms: hot flashes (vasomotor), paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and stinging. Each symptom on the Kupperman index was rated on a scale from 0 to 3 for no, slight, moderate, and severe complaints. To calculate the Kupperman index, the symptoms were weighted as follows: hot flashes (4X), paresthesia (2X), insomnia (2X), nervousness (2X), and all other symptoms (1X). The highest potential score is thus 51. This index has been used widely in the studies of menopausal symptoms so its validity is confirmed [23-25].

**Analysis**

The statistical analysis was performed with SPSS software ver. 16. We used Mauchlys and ANOVA test to evaluate the consistency of the statistical data (p-value of ≤/001).
Results

This study was conducted on 69 eligible women, who were divided into three groups (23 patients in each group). From the participated patients, 67 of them were married and 2 were single. They were aged between 35-69 years old. The average age of the participants was 46.6 ± 8.7 SD (in terms of years). The average time from the last menstrual period was 19.5 ± 3.9 SD (in terms of months). The average Body Mass Index (BMI) of the patients was 27.05 ± 5.2 SD.

In general, from all three groups before the intervention, 21.7% were asymptomatic while 33.3% had severe symptoms. But, at the end of the study all of the patients had no severe symptoms, 89.9% were asymptomatic, and mild symptoms of hot flashes remained in only 7% of patients.

We used Blat Kuperman scale to measure the symptoms of menopause. So including factor of four, the average rate of hot flashes in the three groups before the intervention was 22.63 ± 1.24 SD and at the end of the study it reached to 2.56 ± 0.39 SD with a significant reduction. All eleven variables related to each group (hot flashes, numbness, insomnia, nervousness, severe sadness, dizziness, weakness, muscle pain or arthritis, headaches, heart palpitations and tingling of the skin) had a significant decrease.

In the first group in which the patients had used one capsule of piascledine per day, the average number of Kuperman scale (including eleven variables) before and after intervention was 21.82 ± 2.20 and 7.69 ± 1.33 SD respectively which shows a significant reduction (Table 1).

Table 1. Comparison of BKM index before and after intervention in the first group.

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std. deviation</th>
<th>Std. error mean</th>
<th>95% confidence interval of the difference</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td></td>
<td>Upper</td>
</tr>
<tr>
<td>Pair 1</td>
<td>Prior</td>
<td>14.13043</td>
<td>6.06758</td>
<td>1.26518</td>
<td>11.50662</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the second group in which the patients had used two capsules of piascledine per day the average number of Kuperman scale before and after intervention was 24.69 ± 1.95 SD and 6.28 ± 5.6 SD respectively which shows a significant reduction (Table 2).

Table 2. Comparison of BKM index before and after intervention in the second group.

<table>
<thead>
<tr>
<th>Mean</th>
<th>N</th>
<th>Std. deviation</th>
<th>Std. error mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1</td>
<td>Prior</td>
<td>24.6957</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.39746</td>
<td>1.95951</td>
</tr>
<tr>
<td>Post</td>
<td></td>
<td>6.2899</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.69924</td>
<td>0.56283</td>
</tr>
</tbody>
</table>

In the third group in which the patients had received hormone replacement therapy, the average number of Kuperman scale before and after intervention was 62 ± 38 SD and 21.39 ± 2.29 SD respectively which shows a significant reduction (Table 3).

Table 3. Comparison of BKM index before and after intervention in the third group.

<table>
<thead>
<tr>
<th>Mean</th>
<th>Std. deviation</th>
<th>Std. error mean</th>
<th>95% Confidence interval of the difference</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td></td>
<td>Upper</td>
</tr>
<tr>
<td>Pair 1</td>
<td>Prior</td>
<td>20.76812</td>
<td>11.43644</td>
<td>2.38466</td>
<td>15.82263</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

According to ANOVA test, the rate of hot flushes related to each group was not significantly different before the intervention. But after three months of intervention, the rate of hot flashes of third group (who received hormone replacement therapy) was significantly different compared to first and second groups (P-value ≤ 0.05). Reduction in the rate hot flashes was not significantly different between the first and second groups (Table 4).

Table 4. Comparison of the hot flashes between 3 groups.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>(I) Drug</th>
<th>(J) Drug</th>
<th>Mean difference (I- J)</th>
<th>Std. error</th>
<th>Sig.</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum q10</td>
<td>Pias 1 in every day</td>
<td>Pias 2 in every day</td>
<td>-2.86957</td>
<td>3.05368</td>
<td>0.351</td>
<td>-8.9664 to 3.2273</td>
</tr>
</tbody>
</table>
Then, the differences in the numbers of Kuperman scale were determined in all three groups before and after the intervention. Accordingly, the reduction of symptoms in both groups using piascledine was very sensible. However, the difference between these two groups is not significant. Meanwhile, the difference between the groups taking piascledine and the group receiving hormone replacement therapy was significant. While the reduction rate of symptoms related to the second and third groups is not meaningful (Table 5).

**Table 5. Comparison of the mean differences of Blatt_Kuperman index between 3 groups.**

<table>
<thead>
<tr>
<th>(I) drug</th>
<th>(J) drug</th>
<th>Mean difference (I-J)</th>
<th>Std. error</th>
<th>Sig.</th>
<th>95% Confidence interval</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pias 1 in every day</td>
<td>Pias 2 in every day</td>
<td>-4.27536</td>
<td>2.69626</td>
<td>0.118</td>
<td>-9.6586</td>
<td>1.1079</td>
<td></td>
</tr>
<tr>
<td>Srojen</td>
<td>Pias 1 in every day</td>
<td>-6.63768*</td>
<td>2.69626</td>
<td>0.016</td>
<td>-12.0209</td>
<td>-1.2544</td>
<td></td>
</tr>
<tr>
<td>Pias 1 in every day</td>
<td>Pias 2 in every day</td>
<td>4.27536</td>
<td>2.69626</td>
<td>0.118</td>
<td>-1.1079</td>
<td>9.6586</td>
<td></td>
</tr>
<tr>
<td>Srojen</td>
<td>Pias 1 in every day</td>
<td>-2.36232</td>
<td>2.69626</td>
<td>0.384</td>
<td>-7.7456</td>
<td>3.0209</td>
<td></td>
</tr>
<tr>
<td>Srojen</td>
<td>Pias 2 in every day</td>
<td>6.63768*</td>
<td>2.69626</td>
<td>0.016</td>
<td>1.2544</td>
<td>12.0209</td>
<td></td>
</tr>
<tr>
<td>Pias 1 in every day</td>
<td>Pias 2 in every day</td>
<td>3.63232</td>
<td>2.69626</td>
<td>0.384</td>
<td>-3.0209</td>
<td>7.7456</td>
<td></td>
</tr>
</tbody>
</table>

*The mean difference is significant at the 0.05 level.

**Discussion**

Understanding menopause-associated pathophysiology and developing new strategies to improve the treatment of menopausal-associated symptoms is an important topic in the clinic [21]. Both hormonal and non-hormonal treatments are available for management of the symptoms. There are few studies which have shown the disadvantages of HRT in menopause women. The study of Schumacher et al. conducted in 2003, shows that Estrogen plus progestin therapy increased the risk for probable dementia in postmenopausal women aged 65 y or older [22].

Kim et al. worked on the effect of complementary and alternative therapy on the climacteric period. They find out that hormone replacement therapy increases the potential risk of thrombosis, cerebral infarction and breast cancer [23]. They also mentioned that finding a new alternative for HRT in management of menopause symptoms is an important concern of nowadays.

Epidemiological studies have shown that some of the diseases are more common in the West (including breast, endometrial, colon and prostatic cancers) which are less visible in East Asia that is due to consumption of phytoestrogens such as soy [24]. In a study conducted by Rua et al. it reveals that phytoestrogens appear to reduce the frequency of hot flushes in menopausal women, without serious side-effects [25].

Piascledine is an herbal medicine derived from avocado and soy and almost all the related researches to the piascledine has concentrated on its effects on arthritis, rheumatoid arthritis and osteoarthritis [26-29]. Laurent et al. worked on the relationship between osteoarthritis and nutrition, they have used two different doses of piascledine, 300 and 600 mg per day [30].
In the Appelboom et al. study also which conducted in 2011 on the people with Knee Osteoarthritis and they have used two different doses of piascledine, 300 and 600 mg per day [31]. So the use of piascledine twice a day is permitted and it has no side effects.

Only in one study conducted by Panahi et al. the effects of conventional HRT on the treatment of hot flush was compared with piascledine, they also evaluate the safety of piascledine in relieving postmenopausal symptoms. The patients in that open label clinical trial, randomized to receive piascledine capsule 1 mg or HRT (0.625 mg oral daily conjugated estrogen tablets, plus 2.5 mg continuous oral daily medroxy progesterone acetate tablets) for 2 month. They revealed that due to low HRT compliance and its possible risks in long period of time and considering the same activity of soybean supplement and HRT in relieving the hot flush as menopausal symptoms in women, it seems that soybean supplements can be an alternative therapy to hormone [20]. Their findings were compatible with our results.

In the recent study we compared the effect of two different doses of piascledine (300 and 600 mg) with hormone therapy in menopause women. And according to the results, all three groups had a significant reduction in the symptoms related to the menopause.

A significant difference was seen in all groups, so that the hormone therapy had the greatest effect, then in the second group that received piascledine twice a day the symptoms became disappear and finally in the first group received a capsule of piascledine daily the symptoms reduced. The important issue is that the use of piascledine was associated with no complication or side effect such as spotting or vaginal bleeding (the symptoms that we may see in HRT).

The patients using piascledine also doesn’t have any concern about the different kinds of cancers related to the hormone therapy, Heart disease or thrombosis so they can confidently use this drug to reduce menopause symptoms.

Conclusion

We found that a higher dosage of piascledine leads to a significant reduction in hot flushes rate and according to the effectiveness and also lack of side effects related to the higher dose of piascledine, it seems to be an appropriate alternative for hormone replacement therapy to treat the menopausal symptoms in high dosage.

Acknowledgements

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Financial and Competing Interests Disclosure

The authors report no conflicts of interest.

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25. Rua I, Centro BR. Phytoestrogens appear to reduce the frequency of hot flushes in menopausal women, without serious side-effects. Afr J Pharm Pharmacol 2014; 1071-1087.


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