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Effect of Soy Isoflavones Compared to Estradiol Valerate in Menopausal Women assessed by Menopause Quality of Life Questionnaire

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Abstract

BACKGROUND: There has recently been a global effort to develop preparations that aim for benefits of hormone replacement therapy with minimal discomfort or risk while isoflavones administration found to relieve complaints related to menopause and has been widely carried out.

AIM: The aim of the study is to determine the effect of soy isoflavone compared to estradiol valerate administration in postmenopausal women assessed by the Menopause Quality of Life (MENQOL) questionnaire.

METHODS: This is an experimental study with pre-post test non-randomized design using data from postmenopausal women who were divided into two groups, namely, group I Estradiol Valerate group which is 16 menopausal women were given Estradiol Valerate and group II Soy Isoflavone Supplements group which is 16 menopausal women were given Soy Isoflavone Supplements.

RESULTS: It was found that in estradiol valerate group, total MENQOL value before estradiol valerate administration was 81.56 ± 19.77, and after administration was 74.55 ± 16.82 with p = 0.002, which indicates there is a significant total MENQOL score difference before and after administration estradiol valerate. In the soy isoflavone group, the total MENQOL scores before soy isoflavone administration were 91.0 ± 16.31, and after administration was 83.08 ± 13.85 with p = 0.001, which indicated that there was a significant total MENQOL score difference between before and after administration soy isoflavone.

CONCLUSION: In comparison of menopausal complaints based on MENQOL scale in Estradiol Valerate and Soy Isoflavone groups after intervention, it was shown that there were significant differences in total MENQOL value after intervention.

Introduction

Menopause is a woman's lifetime when ovaries lose their reproductive function, often accompanied by various symptoms. However, only hot flushes and vaginal dryness have been consistently associated with this life stage [1]. Hot flushes can be effectively treated with hormone replacement therapy (HRT) [2]. Recently, isoflavones from soy, black cohosh, and red clover have been reported extensively which is widely used to relieve hot flushes in menopause, but its efficacy remains largely unknown [3].

Research conducted by Siregar in 2014 and 2016, stated that there are several symptoms experienced by perimenopausal and postmenopausal women. Perimenopausal women often complain joint and muscle pain (84%), depression and mood disorders (68%), physical and mental fatigue (68%), then vasomotor symptoms which also often occur in women 45–50 years old (96.1%) [4]. Methods that can be used to assess postmenopausal women quality of life is Menopause Specific Quality of Life Questionnaire (MENQOL) which was introduced in 1996 by Hildrich from Canada as an instrument to assess health-related quality of life in post-menopausal period [5].

Women are reluctant to use HRT mainly because of unwanted side effects (such as irregular bleeding) and concerns about safety (especially potential increased breast cancer risk). Therefore, there has recently been a global effort to develop preparations that aim for the benefits of HRT with minimal discomfort or risk [6].

In recent years, research on phytoestrogens and other herbal plants has been increasingly in demand because of their benefits in reducing menopausal complaints. Isoflavone is a content that is mainly found in soybeans and their products. Isoflavones are included in phytoestrogens because they have an estrogenic effect. Indonesia is one of the Asia countries that had high soybeans consumption and their processed products.

Isoflavones administration to relieve complaints related to menopause has been widely carried out and provides benefits for lipid levels, cardiovascular protection, and osteoporosis protection [7].

Methods

This research is an experimental study with pre-post test non-randomized design using data from postmenopausal women who were divided into two groups, namely, group I Estradiol Valerate group which is 16 menopausal women were given Estradiol Valerate and group II Soy Isoflavone Supplements group which is 16 menopausal women were given Soy Isoflavone Supplements.

Research was carried out at Mutiara Diski Clinic Medan for 3 months starting from September 2020 to December 2020. This research was carried out after ethical clearance approval from the ethics committee. Inclusion criteria for research sample were willing to participate in this research and have signed consent form; without menstruation for at least >12 consecutive months; never had ovarian removal surgery/early menopause; not or have never used hormone replacement therapy; does not suffer any malignancy; and exclusion criteria which were refusing to participate in this research; lost Follow-Up or withdrawal from this research; have a history of soybeans allergy; early menopause and surgical menopause; have a history of gynecological, metabolic, cardiovascular and malignancies and damaged blood serum.

Characteristics data were obtained through history taking and physical examination. Furthermore, required data collection is carried out based on interviews. Withdrawn 5 mL of blood from median cubital vein than was put into a plain tube by laboratory where blood in the tube could last up to 24 h before arriving at laboratory using a cooler box to check serum estradiol levels. After that, intervention was given which is soy isoflavone and estradiol valerate. After consuming it for 12 weeks, the serum estradiol level was rechecked.

The data will be analyzed descriptively to assessed frequency distribution of research variables. The mean difference between variables was tested with T-Independent test. The relationship between characteristic variables and menopause was tested with Shapiro-Wilk normality test, then analyzed to assessed correlation of estradiol valerate and soy isoflavone for menopause symptoms using Pearson correlation test with a significance p value < 0.05. The confidence interval of this research is 95%.

Results

After conducting an experimental study at Mutiara Diski Clinic Medan for 3 months on 32 research samples with 16 samples each for estradiol valerate and soy isoflavone groups that met inclusion and exclusion criteria, data were documented, tabulated, and statistically analyzed.

The results of Shapiro-Wilk normality test show that age data are normally distributed (display the mean ± SD) while systole and diastole are not normally distributed (display median values, min-max). The two intervention groups were balanced, where there were no differences in characteristics based on parity, menopause duration, and Body Mass Index, systolic and diastolic blood pressure ($p > 0.05$) but did not differ by age ($p < 0.05$) (Table 1).

Using the Wilcoxon test, the results showed that there were significant differences in total MENQOL scores, vasomotor, psychosocial, and physical complaints in the estradiol valerate group, but not in sexuality complaints. For soy isoflavone group, there were significant differences in total MENQOL scores, psychosocial and physical complaints, but no significant differences for vasomotor complaints and sexuality (Table 2).

Psychosocial domain and physical domain were significant between administration of estradiol valerate and soy isoflavone before intervention, while vasomotor and sexual domain did not show a significant difference between the administration of estradiol valerate and soy isoflavone. Psychosocial domain and physical domain were significant between administration of estradiol valerate and soy isoflavone after intervention, while vasomotor domain and sexual domain did not show a significant difference between the administration of estradiol valerate and soy isoflavone after intervention (Table 3).

Paired T-test results showed that there was a significant difference in estradiol levels before and after intervention with estradiol valerate ($p < 0.05$). Paired T-test results showed that there was no significant difference in estradiol levels before and after intervention with soy isoflavone ($p > 0.05$) (Table 4).

Shapiro-Wilk normality test showed that estradiol levels before and after intervention showed mean ± SD normally distributed in both groups ($p > 0.05$). The results of the unpaired T-test showed that there was no difference in estradiol levels before intervention in both groups as well as estradiol levels after intervention ($p > 0.05$) (Table 5).

Discussions

Estrogen levels and MENQOL scores were strongly correlated (p = 0.029) with negative correlation of −0.349 and moderate strength. This indicates estrogen levels decrease, increasing overall MENQOL domain score which means decrease in postmenopausal women quality of life. A strong correlation was found between estradiol and psychological dimensions in MENQOL domain, (p = 0.029), which means that decreased estradiol levels were associated with increase psychomotor symptoms such as decreased memory, anxiety and decreased skills in postmenopausal women. In addition, MENQOL domain scores are also influenced by age and hormonal systems. The mean scores for four domains of MENQOL questionnaire were 5.24 ± 3.21; 13.49 ± 4.23; 36.93 ± 7.58 and 7.68 ± 2.48 for vasomotor, psychosocial, physical, and sexual domains, respectively [8].

Table 1: Characteristics of research samples based on estradiol valerate and soy isoflavone groups

Characteristics	*Estradiol valerate* Mean ± SD	*Soy isoflavone* Mean ± SD	p-value
Age (years old)	56.06 ± 2.35	53.81 ± 2.34	0.011[#]
Systolic Blood Pressure (mmHg)	120.31 ± 7.18	117.19 ± 7.52	0.305[#]
Diastolic Blood Pressure (mmHg)	79.06 ± 5.23	77.19 ± 6.05	0.445[#]
	Estradiol valerate n (%)	*Soy isoflavone* n (%)	p*value
Parity			
Primipara	0 (0)	3 (100)	0.113*
Multipara	16 (55)	13 (45)	
Menopause Duration (years)			
1–2	1 (50)	1 (50)	1.0**
3–4	5 (50)	5 (50)	
>5	10 (50)	10 (50)	
Body Mass Index (BMI)			
Normal	14 (61)	9 (39)	0.057*
Overweight	2 (22)	7 (88)	

[#]t-test *independent*, **Chi-square* test, ***Korelasi pearson* test

Xue *et al.* showed that MENQOL after intervention were all significantly lower than before intervention. This indicated that MENQOL in five groups was significantly different (p < 0.01), CEE ± MPA (Conjugated estrogen and medroxyprogesterone acetate) group experienced the most decrease (84 ± 3) [9]. Results with four daily doses of E2/P4 (17b-estradiol and progesterone) (n = 591) and compared with placebo (n = 135). In all 5 growth models, effects on total MENQOL score and vasomotor domain were significantly associated with frequency and severity of VMS changes observed over 12 weeks (all, p < 0.001). Treatment-mediated effects on MENQOL via VMS frequency and severity model were found to be significant. Similar results were also found with the Medical Outcomes Study-Sleep total score and sleep problem index [10].

Table 2: Effect of Estradiol Valerate and *Soy Isoflavone* administration on menopausal complaints based on MENQOL scale

Paramater	*Estradiol Valerate* group		p-value[a]
	Before intervention	After intervention	
Total MENQOL score	81.56 ± 19.77	74.55 ± 16.82	0.002[a]
Vasomotor	6.06 ± 2.46	5.62 ± 2.09	0.020[a]
Psycosocial	17.75 ± 5.14	16.62 ± 4.80	0.010[a]
Physical	53.25 ± 9.92	48.12 ± 8.21	0.002[a]
Sexual	4.5 ± 2.25	4.19 ± 1.72	0.180[a]
Paramater	*Soy Isoflavone* Group		p-value[a]
	Before intervention	After intervention	
Total MENQOL score	91.0 ± 16.31	83.08 ± 13.85	0.001[a]
Vasomotor	5.69 ± 2.18	5.50 ± 2.13	0.083[a]
Psycosocial	23.19 ± 5.44	22.15 ± 4.88	0.027[a]
Physical	56.75 ± 6.60	50.06 ± 4.75	0.001[a]
Sexual	5.37 ± 2.09	5.37 ± 2.09	1.000[a]

[a]Wilcoxon test, [##]t-test *dependent*

A research showed a significant improvement in the Menopause-Specific Quality of Life (MENQOL) domain after EPT (estradiol/norgestimate) administration compared to placebo (p < 0.001) and Heart and Estrogen/Progestin Replacement Study (HERS) trial showed improvements in mental health. and depressive symptoms in sample receiving EPT (CEE/MPA) compared with placebo (p = 0.04 and p = 0.01, respectively) for women who had hot flashes at baseline, but not for those without hot flashes.

Table 3: Comparison of mean menopausal complaints based on MENQOL scale in Estradiol Valerate and Soy Isoflavone groups before and after intervention

Before intervention	*Estradiol Valerate* group	*Soy Isoflavone* group	p-value
Total MENQOL score	81.56 ± 19.77	91.0 ± 16.31	0.001[a]
Vasomotor	6.06 ± 2.46	5.69 ± 2.18	0.060[a]
Psycosocial	17.75 ± 5.14	23.19 ± 5.44	0.020[a]
Physical	53.25 ± 9.92	56.75 ± 6.60	0.032[a]
Sexual	4.5 ± 2.25	5.37 ± 2.09	0.120[a]
After intervention	*Estradiol Valerate* group	*Soy Isoflavone* group	p-value
Total MENQOL score	74.55 ± 16.82	83.08 ± 13.85	0.002[a]
Vasomotor	5.62 ± 2.09	5.50 ± 2.13	0.087[a]
Psycosocial	16.62 ± 4.80	22.15 ± 4.88	0.003[a]
Physical	48.12 ± 8.21	50.06 ± 4.75	0.047[a]
Sexual	4.19 ± 1.72	5.37 ± 2.09	0.120[a]

[a]Wilcoxon test, [##]t-test *dependent*

Bazedoxifene (BZA) 20 mg/CE 0.45 and 0.625 mg showed clinically significant improvements of vasomotor function and total MENQOL score at 12 weeks compared with placebo (p < 0.001). Significant improvements in sexual function scores were observed after administration of BZA 20 mg/CE 0.625 mg and for both doses of BZA/CE compared with placebo (p < 0.01). BZA 20 mg/CE 0.625 mg also showed significant improvement vs placebo in physical function scores and psychosocial scores (p < 0.0) [11].

Table 4: Frequency Distribution based on Mean ± SD Estradiol Levels before and after intervention

Type of intervention	Estradiol Levels		p-value
	Before intervention	After intervention	
Estradiol valerate Mean ± SD	37.40 ± 21.55	49.20 ± 26.98	0.003[##]
Soy isoflavone Mean ± SD	42.35 ± 23.59	51.86 ± 23.10	0.071[##]

[##]t-test *dependent*

Lee *et al.* study showed that Kupperman index score decreased in both isoflavone group (−7.0 ± 15.8, P = 0.0074) and placebo group (−6.3 ± 14.6, P = 0.0064) during intervention, but there was no significant difference between two groups. The MENQOL scores decrease was significant in isoflavone group (−0.6 ± 0.5) and placebo group (−0.6 ± 0.4), with a significant difference between groups (p = 0.0228). The subscale scores for MENQOL were 1.51 ± 1.42 for vasomotor, 0.80 ± 0.62 for psychosocial, 0.89 ± 0.59 for physical,

Table 5: Frequency Distribution based on Mean ± SD Estradiol Level in each group based on type of intervention

Estradiol levels	*Estradiol valerate* Mean ± SD	*Soy isoflavone* Mean ± SD	p-value
Before Intervention	37.40 ± 21.55	42.35 ± 23.59	0.540[#]
After Intervention	49.20 ± 26.98	51.86 ± 23.10	0.767[#]

[#]t-test *independent*

and 1.56 ± 1.64 for sexual in isoflavone group. After 12 weeks, scores decreased to 0.75 ± 1.02 (−0.76 ± 1.13 change) for vasomotor, 0.48 ± 0.50 (−0.32 ± 0.52 change) for psychosocial 0, 51 ± 0.49 (−0.38 ± 0.5 change) for physical, and 0.91 ± 1.40 (−0.65 ± 1.21 change) for sexual in isoflavone group [12]. A significant decrease in\vasomotor, physical, and sexual domain scores of MENQOL and significant increase in all Female Sexual Function Index (FSFI) domain scores were observed in treatment group after 12 months. This study shows that combination of isoflavones, calcium, Vitamin D, and inulin may exert a beneficial effect on menopausal symptoms, sexual function, and quality of life [13].

Peng *et al.* study showed that phytoestrogen group scored significantly higher for body pain (mean difference = 3.85, 95% confidence interval [CI] = [1.14, 6.57], p < 0.01), mental health (mean difference = 4.01, 95% CI = [1.49, 6.57], p < 0.01), and role limitations caused by emotional problem domains (mean difference = 3.83, 95% CI = [1.81, 5.85], p < 0.01). No statistically significant difference was obtained from MENQOL survey (vasomotor domain mean difference 0.14, 95% CI = [−0.08, 0.36], p = 0.20; physical domain mean difference 0.20, 95% CI [−0.08, 0.48], p = 0.15; psychological domain mean difference 0.10, 95% CI [−0.26, 0.07], p = 0.27; sexual domain mean difference −0.17, 95% CI [−0.42, 0.09], p = 0.19). Current evidence does not support phytoestrogen supplementation that improves postmenopausal quality of life [14].

Lumbanraja *et al.* found a difference value of most bothersome symptoms and value of FSFI in soy isoflavone group before and after intervention (p = <0.001; p = 0.031) and there was no difference in vaginal maturation index value in soy isoflavone group. Before and after intervention (p = 0.079). Giving soy isolavone for 90 days can reduce urogenital complaints and improve sexual function in menopausal women without affecting the vaginal maturation index [15].

Conclusion

In comparison of menopausal complaints based on MENQOL scale in Estradiol Valerate and Soy Isoflavone groups after intervention, it was shown that there were significant differences in total MENQOL value after intervention, psychosocial domain, and physical domain between estradiol valerate and soy isoflavone administration, while vasomotor domain and sexual domain did not show a significant difference.

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