



THE EFFECT OF ELECTROACUPUNCTURE COMPARED WITH HORMONAL THERAPY (TIBOLONE) ON THE CLIMACTERIC SYMPTOMS, HORMONAL CHANGES (ESTRADIOL, ESTROGEN RECEPTOR), AND LIPID PROFILE IN MENOPAUSAL WOMAN

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ABSTRACT

Background. Loss of estrogen in menopausal women can cause vasomotor symptoms, cognitive impairment, and impact the quality of life. Hormonal therapy (Tibolone) is the most common therapy despite being very expensive with harmful side effects (endometrial bleeding, breast cancer). Therefore a safe and beneficial alternative treatment is always sought, namely acupuncture. This study aimed to compare the effects of electroacupuncture with Tibolone on climacteric symptoms, hormonal changes (estradiol level, estrogen receptor), and lipid profile in menopausal woman. **Methods.** A Randomized Clinical Trial study. Subjects were divided into two groups: electroacupuncture (n=37) and Tibolone therapy (n=37). Unpaired t-test is used to test the difference between the result of electroacupuncture and Tibolone. To know the effect of acupuncture and Tibolone on lipid profile, ANCOVA Multivariate Analysis is used. **Results.** There is no significant difference between electroacupuncture and Tibolone on climacteric symptoms and level of estradiol ($p > 0,05$) and vaginal estrogen receptor. There is an effect of electroacupuncture and Tibolone on HDL ($p = 0,009, 95\% CI 1,09-7,27$) and Triglyceride ($p < 0,001, 95\% CI 27,97-76,26$). **Conclusion.** There is no difference between electroacupuncture and Tibolone on decreasing climacteric symptoms, and increasing the level of estradiol and vaginal estrogen receptor. There is an effect of electroacupuncture and Tibolone on HDL and Triglyceride.

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INTRODUCTION

Background

Menopause is one of the phase of life that will be experienced by all woman, where there is a decrease in the function of the ovarium that causes the decrease in estrogen level (Andrikoula et al, 2009) (Smith, 2005) (Zhou et al, 2012) (Sturdee, 2008) (Freeman, 2011). The term menopause denotes the period of one year after the cessation of menstruation (Freeman, 2011) (Fritz et al, 2011) (Baziad, 2003) (Lima et al, 2012). The average menopausal age in the western countries such as the United States of America and the United Kingdom is 51,4 years and 50,9 years respectively. The decrease of estrogen level causes the appearance of climacteric symptoms, which includes functional changes in the endocrine system and the central nervous system, and some psychological symptoms (Freeman, 2011) (Fritz et al, 2011) (Sastroasmoro et al, 2004). Climacteric symptoms can cause the disability to work and difficulties in sleeping, therefore reducing the quality of life (Paksi, 1996) (Soewondo, 2001).

Estrogen is composed of three different hormones, which is estron, estradiol, and estriol. Estrogen level increase in ovulation, pregnancy, precog puberty, gynecomastia, testicular atrophy, tumor of the ovary, aand tumor of the adrenal gland. The level will decrease in menopasue, ovarian dysfunction, infertility, Turner syndrome, amenorrhea caused by hypopituitary, anorexia nervosa, stress, and testicular feminization syndrome in woman (Freeman, 2011).

Estrogen receptor (ER) is a protein molecule where the hormone estrogen attached to and works on the target tissues (Fritz et al, 2011). The vagina is rich in estrogen receptors and the decrease in estrogen level during the menopausal transition period can cause the loss of elasticity, vascularization, and al, 2011) in this area. The decreasing estrogen production in menopause causes the atrophy of the vulvae, vaginal dryness, irritation, dyspareunia, and recurrent urinary tract infection (Fritz et al, 2011) (Baziad, 2003).

The decrease of estrogen level in perimenopausal woman will cause the change in one of the neurotransmitter, which is catecholamine, that is needed for dopamine and norepinephrine metabolism-neurotransmitters which play a role in mood, behavior, and motoric activity; the same as the

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function of the hypothalamus and hypophyses glands (Andrikoula *et al*, 2009) (Freeman *et al*, 2011) (Fritz *et al*, 2011) (Baziad, 2003). Estrogen deficiency also contributes to increased vasoconstriction that will cause an increase in the blood pressure and the risk of cardiovascular disease (Vincent *et al*, 2007).

The decrease or loss of estrogen can cause vasomotor symptoms, such as hot flushes, sleep disturbance, mood disturbance, depression, urinary tract and vaginal atrophy, and the increase in the risk of chronic diseases such as osteoporosis, cardiovascular disease, and the decrease of cognitive function. Hot flushes can appear as a sudden sensation of heat on the chest that radiates to the neck and face, usually accompanied by fatigue, palpitation, sweating, and reddened skin (Sastroasmoro *et al*, 2004).

Physiological estrogen level also plays a role in maintaining the lipoprotein profile in woman. During adulthood, the high density lipoprotein (HDL) level is on average higher by 10 mg/dL in woman compared to man and this trend continues until the postmenopausal period. Total cholesterol level and low density lipoprotein (LDL) is lower in premenopausal woman compared to man (Ching *et al*, 2000). After menopause, with the decrease in estrogen level, there is a decrease in HDL level and an increase in total cholesterol level (Baziad, 2003).

There are several choices of therapy to reduce the hot flush symptoms, including hormonal therapy, drugs (bromocriptine, naloxone, selective serotonin reuptake inhibitors (SSRIs)), counseling, and hormone replacement therapy (HRT)-for example Tibolone (Baziad, 2003). HRT is one of the type of drugs used most often by postmenopausal woman in developed countries (Anderson *et al*, 2004).

Tibolone is a synthetic steroid that contains estrogen, androgen, and progestogenic preparat. After consumption, Tibolone is converted swiftly in the liver and intestines into three metabolites: 3 α -hydroxy tibolone dan 3 β -hydroxytibolone that have estrogenic effects and Δ 4-isomer that has progestogenic and androgenic effects. Tibolone is a selective tissue estrogenic activity regulator (STEAR). Tibolone has estrogenic effect on the bone and vaginal tissue. In endometrial tissue, Δ 4-isomer functions as progesterone, but in the brain and liver tissue, it has an androgenic effects.

Tibolone is very effective in relieving hot flushes, increasing mood and libido, and improving sexual complaints (Anderson *et al*, 2004). According to Genazzani *et al*, Tibolone is proven to increase β -endorphine level in the pituitary and plasma, which shows that Tibolone can improve mood in woman. Centrally, 25, mg daily dose of Tibolone can significantly suppress the follicle stimulating hormone (FSH) and leutenizing hormone (LH) secretion in menopausal woman. Tibolone administration in menopauseal woman is proven to be able to improve lipid profile by increasing HDL level and reducing LDL and cholesterol levels (Vincent *et al*, 2007) (Ching *et al*, 2000) (Anderson *et al*, 2004).

Acupuncture is a form of therapy where a needle is inserted into certain points on the skin in order to reduce pain and cure some health conditions (Kiswojo *et al*, 2010) (Kershaw *et al*, 2004). This method is proven to be able reduce hot flushes and other symptoms that appear during menopausal period. In

the hands of a competent practitioner, acupuncture is a safe procedure with very few contraindications or complications. The most important thing in the safety of acupuncture is the prevention of infection, including good working environment, the practitioner's hand hygiene, cleaning the puncture loation, sterile needles and equipments, and aseptic technique (World Health Organization, 1996).

One of the method of acupuncture stimulation is by using electric current, which is known as electroacupuncture (Kiswojo *et al*, 2010) (Kershaw *et al*, 2004). Electroacupuncture is a comprehensive procedure with the purpose of performing examination or therapy based on acupuncture science by using electrical stimulation device (Mayor, 2007).

The research on rats that had undergo ovariectomy and in menopausal woman by using the CV4 Guanyuan, SP6 Sanyinjiao, and EX-CA1 Zigong acupuncture points proves that there is an increase in estradiol level through the regulation of hypothalamus-pituitary-ovary (HPO) axis (Chen, 1997). The objective of this research is to determine the difference of the effect of electroacupuncture and Tibolone on the climacteric symptoms in menopausal woman. This research will try to determine wether electroacupuncture on the SP6, EX-CA1, CV3, and CV4 acupuncture points can reduce climacteric symptoms, affecting reproduction hormones (estradiol, ER), and whether electroacupuncture on the ST36 and ST40 acupuncture points can regulate the lipid profile in menopausal woman.

METHODS

This research is done after obtaining ethical clearance from the Health Researches Ethics Committee of Faculty of Medicine Universitas Padjadjaran, Bandung, and Faculty of Medicine Universitas Indonesia / RSUPN dr. Cipto Mangunkusumo, Jakarta. The research design is a randomized clinical trial, single blind. This research period is from September 2014 to March 2015 at the Medical Acupuncture Polyclinic of RSUPN dr. Cipto Mangunkusumo hospital, Jakarta. The available population is menopausal woman that undergo examination in the Obstetrics and Gynecology Polyclinic of RSUPN dr. Ciptomangunkusumo hospital.

The inclusion criteria of this research is that the subject has been diagnosed as menopausal woman experiencing climacteric symptoms, 45 to 55 years of age, had been in a menopausal period for one to two years, cooperative, and is willing to follow the research procedure. The exclusion criteria in this research are wounds, infection, allergic reactions, and/or tumor on the acupuncture point locations that will be used in the research, using drugs or herbal medication to relief the climacteric symptoms, menopause due to ovariectomy and/or hysterectomy, and having Diabetes Mellitus (Blood Sugar \geq 200 mg.dL). The subject is deemed to have dropped out if she does not come for the therapy sessions for times during the research duration or using drugs or herbal medication to relief the climacteric symptoms.

All of the subjects is allocated randomly into two groups, electroacupuncture group and Tibolone group, using computer based random allocation program.

For the treatment group, the participant lie in supine position, then the acupuncture point locations is determined. In this

research, the acupuncture points CV4 Guanyuan, CV3 Zhongji, SP6 Sanyinjiao, ST36 Zusanli, ST40 Fenglong, dan EX-CA1 Zigong is used. Aseptic method is applied on the acupuncture point locations then acupuncture needle is inserted into the skin until the needling sensation (tingling, numbness) is achieved; after that the needle is connected to the stimulator electrode and retained for 30 minutes. The therapy session is done twice a week with the total of 16 sessions. For the hormonal therapy group, Tibolone is administered for three months.

The evaluation is done by evaluating the climacteric symptoms (using Greene climacteric scale, consisting of three independent main symptom measurements: psychological symptoms, somatic symptoms, and vasomotor symptoms) (Chen, 1997), estradiol level, lipid profile (total cholesterol, HDL, LDL, and triglyceride), and ER. Blood sample before and after the therapy is collected in the form of blood plasma and analyzed using the ELISA method at the Prodia Pusat clinical laboratory, Jakarta. ER examination from the vaginal swab is done using the immunohistochemical method at the Histology Department and Patology Anatomy Department of the Faculty of Medicine Universitas Indonesia / RSUPN dr. Ciptomangunkusumo hospital, Jakarta.

The data obtained is analyzed using the SPSS 16.0 program and shown descriptively. The categoric data is shown in frequency and percentage, while the numeric data is shown in mean, median, and the interval value. The analysis for the hypotheses testing is done according to each hypothesis. The hypothesis testing for categoric data that compares the proportion of two groups is done in a bivariate way using chi square test or Fisher's exact test, while for the numeric data that compares the mean value of two groups, the analysis is done using independent t-test or Mann-Whitney test. To analyze the effect of electroacupuncture and Tibolone on the lipid profile (total cholesterol, HDL, LDL, and triglyceride), ANCOVA multivariate analysis test is used.

RESULTS

Table 1 Research subject Characteristics

Variable	Groups		P Value
	Electroacupuncture	Tibolone	
Age	52 (45 - 55)	53 (45 - 55)	p = 0,09
Menopause age	50 (43 - 55)	51 (44 - 53)	p = 0,21
Menopause duration	2 (1 - 2)	2 (1 - 2)	p = 0,09
BMI	26,59 ± 4,11	25,12 ± 2,47	p = 0,06

Independent t-test, *Mann-Whitney test

The research subjects as a whole is in an age range of 45-55 years, age of menopause in the range of 43-55 years, and menopause duration of 102 years. The subjects characteristics, included in it age, menopause age, menopause duration, and BMI, showed no significant difference between the two groups (p>0,005).

Before intervention, the score of climacteric symptoms, estradiol level, lipid profile (HDL, LDL, TG) is not significantly different (p>0,05). A significant difference between the two groups can be observed in the total cholesterol level (p<0,05).

Table 2 Characteristics of Climacteric Symptoms, Estradiol Level, and Lipid Profile Before Intervention

Variable	Groups		P
	Electroacupuncture	Tibolone	
Climacteric symptoms	21 (7 - 45)	22 (16 - 37)	0,343
Estradiol	14,80 (11,70-73,0)	12,8 (11,70-37,70)	0,238
Lipid Profile:			
Total Cholesterol	199 ± 41,62	217,76 ± 30,26	0,038
HDL	53,1 ± 10,82	53,03 ± 10,85	0,449
LDL	130,70 ± 41,08	146,35 ± 32,85	0,075
TG	112 (48 -546)	106 (53 - 304)	0,436

Independent t-test, *Mann-Whitney test TG=Triglyceride

Table 3 Climacteric Symptoms Before and After Intervention Between Two Groups

Climacteric Symptoms	Groups		P
	Electroacupuncture	Tibolone	
Before	22,59±10,05	23,97±5,41	0,343
After	5,31± 3,24	5,05±2,85	0,836

Independent t-test

In the electroacupuncture group, there is a change in the climacteric symptoms score (CGS) from the baseline of 22,59±10,05 to 5,11±3,24 after intervention, a decrease of 17 points. While in the Tibolone group there is a change in the climacteric symptoms score from 23,97±5,41 to 5,05±2,85 after intervention, a decrease of 18 points. Statistically, there is no significant difference between the two groups (p>0,05).

Table 4 Δ Anxiety, Depression, Psychological, Somatic, Vasomotor, and Sexual Dysfunction score between Electroacupuncture Group and Tibolone Group After Therapy

Variable	Groups		P
	Electroacupuncture	Tibolone	
Δ Anxiety score	-4,24 ± 3,328	-3,92 ± 2,228	0,624**
Δ Depression score	-4,11 ± 3,381	-2,76 ± 1,992	0,139*
Δ Psychological score	-8,35 ± 6,075	-6,68 ± 3,606	0,154**
Δ Somatic score	-6,11 ± 3,703	-7,68 ± 3,206	0,084*
Δ Vasomotor score	-1,16 ± 1,405	-2,76 ± 1,234	0,000*
Δ Sexual dysfunction score	-1,84 ± 1,236	-1,76 ± 1,038	0,604*

Independent t-test

As can be seen in the Table 4, of all the climacteric symptoms, which includes psychological, somatic, vasomotor, and sexual dysfunction symptoms, there is a significant difference in the vasomotor and sexual dysfunction score between the two groups (p<0,005)

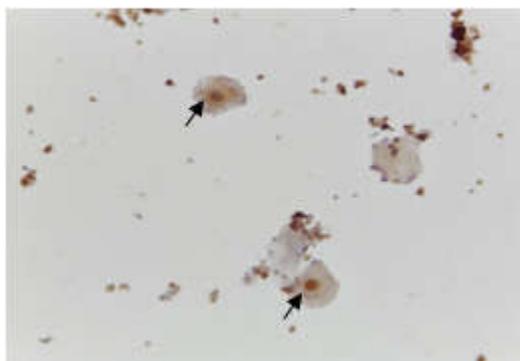
Table 5 Estradiol Level Before and After Therapy between Two Groups

Estradiol Level	Groups		P
	Electroacupuncture	Tibolone	
Before	18,13±11,28	15,46±6,15	0,236
After	20,14±13,16	18,62±8,39	0,650

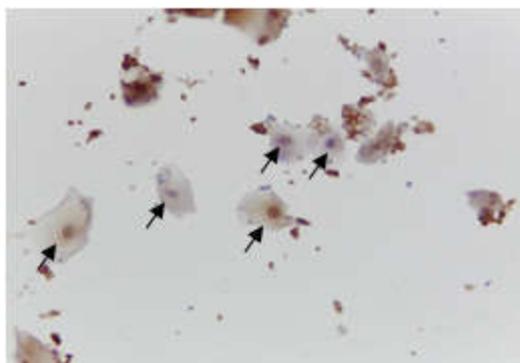
Independent t-test

In the electroacupuncture group, there is a change in the estradiol level from the baseline of 18,13±11,28 to 20,14±13,16 after intervention, while in the Tibolone group there is a change in estradiol level from 15,46±6,15 to 18,62±8,39. Statistically, there is no significant difference between the two groups (p>0,05).

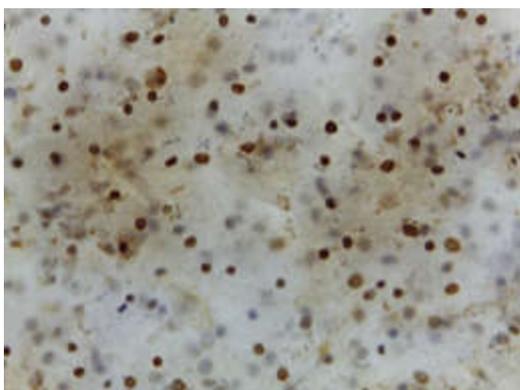
Estrogen Receptor Examination Results



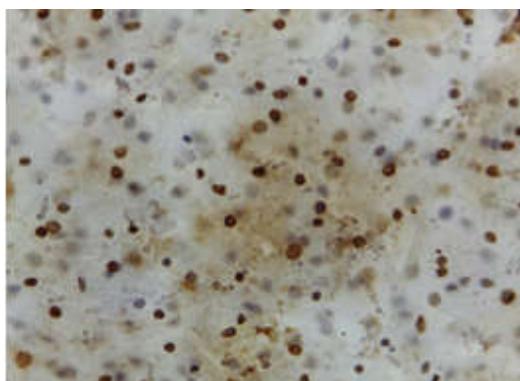
Picture 1 Estrogen receptor percentage before Electroacupuncture: 10%



Picture 2 Estrogen receptor percentage after Electroacupuncture: 20%



Picture 3 Estrogen receptor percentage before Tibolone administration: 30%



Picture 4 Estrogen receptor percentage after Tibolone administration: 50%

From the vaginal swab estrogen receptor examination, it was found that there is an increase in the electroacupuncture group from 10% to 30% and the Tibolone group from 30% to 50%

Table 6 ANCOVA Analysis Results on the Total Cholesterol After Intervention

		Mean±SD	P value	Difference	95% CI
Unadjusted	Acupuncture(n=37)	206,22±45,09	0,449	-7,81	-28,26-12,64
	Tibolone(n=37)	214,03±43,15			
Adjusted ^a	Acupuncture(n=37)	215,09±25,95	0,109	9,94	-2,27-22,15
	Tibolone(n=37)	205,15±25,95			
Adjusted ^b	Acupuncture(n=37)	214,71±24,34	0,116	9,17	-2,32-20,66
	Tibolone(n=37)	205,54±24,34			

^aTotal cholesterol before intervention as confounding variable
^bTotal cholesterol before, HDL before, LDL before, and Triglyceride before intervention as confounding variable

Table 7 ANCOVA Analysis Results on the Total Cholesterol after Intervention

		Mean±SD	P value	Difference	95% CI
Unadjusted	Acupuncture(n=37)	206,22±45,09	0,449	-7,81	-28,26-12,64
	Tibolone(n=37)	214,03±43,15			
Adjusted ^a	Acupuncture(n=37)	215,09±25,95	0,109	9,94	-2,27-22,15
	Tibolone(n=37)	205,15±25,95			
Adjusted ^b	Acupuncture(n=37)	214,71±24,34	0,116	9,17	-2,32-20,66
	Tibolone(n=37)	205,54±24,34			

^aTotal cholesterol before intervention as confounding variable
^bTotal cholesterol before, HDL before, LDL before, and Triglyceride before intervention as confounding variable

Table 8 ANCOVA Analysis Results on the Triglyceride After Intervention

		Mean±SD	P value	Difference	95% CI
Unadjusted	Acupuncture(n=37)	149,43±77,38	0,004	46,7	15,53-77,88
	Tibolone(n=37)	102,73±55,01			
Adjusted ^a	Acupuncture(n=37)	150,31±53,27	<0,001	48,46	23,76-73,16
	Tibolone(n=37)	101,85±53,27			
Adjusted ^b	Acupuncture(n=37)	152,14±51,15	<0,001	52,12	27,97-76,26
	Tibolone(n=37)	100,02±51,15			

^aTriglyceride before intervention as confounding variable
^bTotal cholesterol before, HDL before, LDL before, and Triglyceride before intervention as confounding variable

Based on the results of ANCOVA Multivariate analysis, both electroacupuncture and Tibolone can affect HDL and triglyceride levels in menopausal woman (p<0,05).

Discussion

The purpose of this research is to compare the effect of electroacupuncture and hormonal therapy on the climacteric symptoms, hormonal changes (estradiol level, estrogen receptor), and lipid profile (total cholesterol, HDL, LDL, and triglyceride) in menopausal woman. This research includes 74 participants that is allocated into two groups: electroacupuncture group and Tibolone group.

Based on recent scientific evidence, until the writing of this research, there is no study on vaginal estrogen receptors in menopause woman; this research is the first study on this matter. In this research, an age range of 45-55 year is used. The characteristics of the research subjects include age, menopause age, menopause duration, and body mass index (BMI). Of the four characteristics, there is no significant difference between the two groups (p>0,05), therefore the two groups can be compared.

In this research, either electroacupuncture or Tibolone is just as effective in reducing the climacteric symptoms. In the electroacupuncture group, there is a 17 points change in climacteric symptoms score (CGS), from the baseline of 22,59±10,05 to 5,11±3,24. In the Tibolone group there is also a 18 points change in climacteric symptoms score from 23,97±5,41 to 5,05±2,85.

A study of 53 postmenopausal woman divided into two groups, acupuncture group (n=27) and sham acupuncture group (n=26). Both groups received two sessions of therapy per week with the total of 10 sessions. The climacteric symptoms is assessed by using the menopause rating scale (MRS). After two therapy sessions, there is a significant difference between the two groups ($p < 0,05$). In the acupuncture group, there is a change from the baseline of $23,9 \pm 6,5$ to $9,6 \pm 4,7$; compared to *sham* acupuncture group from the baseline of $21,4 \pm 6,2$ to $20,5 \pm 6,8$ (Sunay *et al*, 2011). In this research, the MRS score is decreased for 17 points, from $22,59 \pm 10,05$ to $5,11 \pm 5,11$. This decrease is larger than Sunay's study, which is 14,3 points.

In a research to compare acupuncture therapy and Tibolone therapy for three months on 46 Chinese woman that has both their ovaries removed, the results showed that there is no significant difference between the two groups. In the acupuncture group, the score for hot flush decreased from $14,21 \pm 2,42$ to $7,69 \pm 1,48$, while in the Tibolone group the score decreased from $15,28 \pm 4,06$ to $3,71 \pm 4,06$ (Conchetto, 1999). Another study also assessed the changes in FSH, LH, and estradiol hormone levels and compare them between the two groups. There is an increase in estradiol level in both groups; in the acupuncture group from $37,1 \pm 8,9$ to $45,4 \pm 7,3$ and in the Tibolone group from $39,4 \pm 7,0$ to $71,5 \pm 13,4$ (Zhou *et al*, 2011).

Tibolone is effective in reducing vasomotor symptoms such as hot flushes and sweating through its estrogenic effect. Tibolone can improve mood, anxiety, and insomnia through endogenous opioid stimulation, especially β -endorphin. Genazzani showed that Tibolone can increase endorphine level in the hypophysis and blood plasma. Mood improvement can also be induced by androgens. Tibolone's effect on mood is mediated by the metabolite Δ^4 - isomer which can be formed locally in the brain by the enzyme 3β -hydroxy steroid dehydrogenase (3β -HSD) isomerase.

A normal ovary is the main source of estrogen production. In postmenopausal woman with a disorder of the ovaries, estrogen is produced using androgen precursors by other tissues. Androgen is a hormone that is needed by the body to produce estrogen through the aromatase enzyme. Aromatase enzyme converts androgens or androstenedione into estron (E1), which is then converted into estradiol (E2) with the help of the enzyme 17β -HSD type 1 and estronsulfatase.

As shown in Table 5, both electroacupuncture and Tibolone increase the estradiol level ($p > 0,05$). From several studies, it is proven that acupuncture increased enzymes that is involved in aromatation processes, therefore increasing the estrogen level. Acupuncture will increase the function of the adrenal glands to produce androgen and dihydroepiandrosterone (DHES) which is a precursor for the formation of other steroids in the brain and peripheral tissues. The enzyme 3β -HSD transforms DHES into and rosteridione which will be carried to extragonadal tissues such as the adipose tissues to be aromatized into the estrogen estradiol. Increased blood estradiol level will bound to the vaginal estrogen receptors and reduce the vaginal atrophy and the symptom of dyspareunia.

Acupuncture point is a sensitive region which when stimulated will activate specific signaling molecules, which will affect the functions of cells that have specific receptors

(cell signaling) in the neuroendocrine-immune system, in order to achieve homeostasis. Acupuncture point is a series of nerve and neuroactive components that is spread along the skin, muscles, and connective tissues which will be activated when acupuncture needle is punctured. The collection of nerve and neuroactive components is termed as a neural acupuncture unit (NAU) which will give a physiological and biochemical responses in the form of the release of neuroactive mediators such as acethylcholine, histamine, substance P, which will work on the corresponding receptors on the cell surface of peripheral afferent fibers. Based on the characteristics of NAU, the mechanism of acupuncture can be divided into:

Local Reaction

Needling causes a microtrauma. After that the tissue will release its mediators in order to repair the damage immediately, therefore starting a cascade of biochemical reactions, which is the release of histamine, kinine, lymphokine, leukotriene, and prostaglandine. The effect is limited locally.

Segmental Reaction

Needling triggers an efferent gamma loop on the ventral horn of the medulla spinalis, which will activate the motoric somatic nerve of the muscles, and the autonomic motoric nerve of the blood vessels and internal organs. Afferent informations is also propagated to the medulla spinalis superiorly and posteriorly, causing muscle reflexes, nociceptive and visceral, along the medulla spinalis from the spinal segment where the impulse is generated. Neurons that is connected to the muscle system consists of a pathway that is known as gamma loop, which is important for the muscle function, although the voluntary motoric signal is caused by the descending pathway from the brain. Regional reaction consisted of the activation of a wide area (2-3 dermatomes) through the reflex loop. These reflexes is the viscerocutaneous reflex, cutaneous visceral reflex, visceromotoric and viscerovisceral reflex, somatomotor reflex, and vegetative reflex.

Central Reaction

According to Le Bars *et al* (1979), there is a neuronal mechanism, the diffuse noxious inhibitory controls (DNIC), which originates from the dorsal reticular subnucleus in the caudal part of the medulla oblongata and will inhibit the gelatinous substance (SG). The needling signal is carried by the somatic afferent fiber into the medulla spinalis and then activate the hypophysis-hypothalamus, which will release β -endorphine into the blood vessels and the cerebrospinal fluid, causing the increase of physiologic analgesia and the homeostasis of various systems, including the immune, cardiovascular, respiratory, and tissue recovery systems. There is also the secretion of adrenocorticotropine hormone (ACTH) and other hormones such as thyrotropine releasing hormone (TRH), growth hormone (GH), antidiuretic hormone (ADH), follicle stimulating hormone (FSH) leutenizing hormone (LH), and other hormones. This hormone can stimulate the release of cortisol which will modify the pain sensation and immune reactions.

The acupuncture points used in this research are CV3, CV4, SP6 and EX-CA1 to stimulate the release of the hormone estrogen, estrogen receptor, and reducing the climacteric symptoms; because the points can regulate the

hypothalamus-hypophysis-gonadal axis. Some studies have proven that acupuncture can affect climacteric symptoms, estradiol level, lipid profile, and estrogen receptor by improving the function of the hypothalamus-hypophysis-ovarium (HPO) axis, increasing the estradiol level, stimulating aromatization of the hypothalamus, regulating the decrease in protein and mRNA expression on the estrogen receptor, modulating the secretion and decreasing the expression level of IL-6 mRNA, and stimulating the release of β -endorphine which will stimulate the Th2 cells to produce IL-10 which will reduce the inflammation reaction (Chen, 1997).

Fat is specifically rich in the aromatas eactivity and obese postmenopausal woman can produce estrone in large quantity. This large number of endogenous estrone gives protection from the vasomotor symptoms and osteoporosis in menopause. The suboptimal increase of the estradiol after 16 sessions of therapy in this research is possibly because not all androstenedione produced by the adrenal glands is aromatized into estrone.

The expression of estrogen α (ER- α) receptors in the ventromedial nucleus of the hypothalamus and arcuate nucleus increase in rats that have undergo ovariectomy which is given electroacupuncture stimulation. Electroacupuncture is proven to significantly increase the mRNA expression of enzymes in the adrenal cortex of the ovariectomized rats, which illustrates the increase of androgen synthesis and dearomatization in the form of estrogen in the extragonadal areas, such as the lipid tissue and liver tissue.

For the examination of the estrogen receptors from the vaginal swab in this research, only two samples can be obtained and prepared using the immunohistochemical method. One sample is obtained for the electroacupuncture group and one for the Tibolone group before and after the intervention. The percentage of estrogen receptor in the Tibolone group sample after the intervention is larger, which is from 30% to 50% (Picture 3 and Picture 4) while in the electroacupuncture group from 10% to 20% (Picture 1 and Picture 2). This is due to the metabolite of Tibolone, 3 α -OH-Tibolone and 3 β -OH-Tibolone, which is estrogenic and can directly affect the vaginal estrogen receptors, and reduce vaginal dryness dyspareunia¹⁹. Aside from the Tibolone metabolites, the androgenic metabolite 4-isomer affects the adrogen receptors in the brain and increase libido. The estrogen receptor examination faced the problem of the difficulty in optimizing the colouring process, therefore only one case in each group can be reported.

Electroacupuncture will increase local estrogen level and improve the expression of hypothalamus estrogen receptor in ovariectomized rats. The improvement of the neuronal response of GnRH to estrogen happened because of a negative feedback of estrogen to the HPO axis, therefore inhibiting the hypersecretion of GnRH due to ovariectomy. The effect of acupuncture on the increase of vaginal estrogen receptor requires longer time compared to Tibolone, because more time is needed to stimulate estrogen locally and centrally.

The needling of acupuncture points will release prostaglandine locally. Prostaglandine will activate PPAR γ to stimulate adipose cells to release adiponectine. Adiponectine will bound to the adiponectine receptor 2 in the liver, and

through the protein G will activate PPAR α which will affect the genetic transcription of lipid metabolism processes in the liver. The use of the points ST36 and ST40 is expected to improve lipid profile through the increase of PPAR.

Some studies showed that acupuncture is quite effective in improving dyslipidemia. Some researches done on the ST40 Fenglong acupuncture point proved that dyslipidemia can be improve by affecting the lipid metabolism to the level of genetic expression. In this research, ANCOVA multivariate test showed that there is an effect of electroacupuncture and Tibolone on the HDL and triglyceride, but there is no effect on total cholesterol and LDL. According to a systematic review (2002) on seven RCTs that studied the effect of Tibolone compared to placebo on the lipid metabolism in menopausal woman, Tibolone can reduce HDL level as much as 34%, triglyceride for 25%, and has no effect on LDL.

In this research, electroacupuncture is still unable to improve lipid profile maximally. One of the possible cause is that this research only used low frequency electroacupuncture, which stimulates the release of β -endorphine therefore able to increase GH and IGF-1 levels, while the research of Zhou used the combination of low and high frequency, where high frequency will release serotonin which is also able to increase the IGF-1 level and activating the PPAR γ that will affect the genetic expression of lipid metabolism. The failure of this research to improve lipid profile is the same as the research by Ismail LAA that showed acupuncture decrease the TNF α , IL-6 and hsCRP, creatinine dan uric acid, total cholesterol and triglyceride, and fasting blood glucose levels; but not the ureum, SGOT, SGPT, HDL, and LDL levels.

It can be concluded in this research that electroacupuncture for 16 sessions or the administration of Tibolone for three months can reduce the climacteric symptoms, most notably the vasomotor symptoms and dyspareunia, and also increasing the estradiol level and regulating the lipid profile.

Research Limitations

This rsearch cannot obtain the result of vaginal swab estrogen receptor examination from all the participants because of the difficulty of optimizing the colouring of the swab samples.

CONCLUSION

The result of this research showed that there is no significant difference between electroacupuncture and Tibolone in reducing the climacteric symptoms and increasing hormonal level (estradiol, estrogen receptor) of menopausal woman. Besides, electroacupuncture and Tibolone also affect HDL and triglyceride, but do not affect LDL and total cholesterol.

Suggestions

Electroacupuncture can be used as a complementary therapy in menopausal woman. Further research is needed to determine the duration of effect of electroacupuncture in reducing the climacteric symptoms.

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