

Relationship between the administration of estradiol valerate 2 mg and norgestrel 0.5 mg and cognitive function which assessed with IQCODE on menopausal paramedic at Adam Malik General Hospital Medan

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SUMMARY: Relationship between the administration of estradiol valerate 2 mg and norgestrel 0.5 mg and cognitive function which assessed with IQCODE on menopausal paramedic at Adam Malik General Hospital Medan.

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Background. Menopause is the cessation of menstruation at least 12 months, begins at the age of 45-50 years and is accompanied by the declined of estrogen and progesterone hormones, causing complaints such as the decline in cognitive function. Hormone replacement therapy such as estradiol valerate and norgestrel can reduce complaints and reduce the risk of dementia.

Objective. To assessed the difference in cognitive function with the administration of estradiol valerate 2 mg and norgestrel 0.5 mg which assessed by IQCODE on menopausal paramedics.

Methods. This study is an experimental quasi research with pre-

post design conducted in July-December 2017. The study subjects were 40 menopausal paramedics at H. Adam Malik General Hospital and selected by consecutive sampling. Study subjects were asked to fill out the IQCODE questionnaire and will be excluded if the result is improvement and no change. Study subjects were asked to consume estradiol valerate 2 mg and norgestrel 0.5 mg for 3 months then cognitive function will be revalued. Data were analyzed using T-paired test.

Results. Out of the 40 study subjects, 2 had improvement and no change, while the other 2 subjects were excluded due to tachycardia and loss to follow-up. The most often encountered characteristics of study subjects were the 50-59 years group (72.2%), multiparous (91.7%), overweight (63.9%) with duration of menopause for 2 years (36.1%). The mean score of IQCODE before and after intervention was 3.59 ± 0.26 and 3.18 ± 0.29 and there was a relationship between administering estradiol valerate and norgestrel with cognitive function.

Conclusion. There was a significant association between administering estradiol valerate 2 mg and norgestrel 0.5 mg with cognitive function ($p < 0,05$).

KEY WORDS: Estradiol valerat - Norgestrel - Cognitive function - Menopause.

Introduction

According to WHO, menopause is the period of cessation of menstruation that occurs at least 12 months due to the ineffectiveness of the ovarian follicles, usually starting at the age of 45-50 years old. During menopause, there are changes in physiology, psychology and hormonal aspects. The menopause

period is characterized by the decrease in the level of estrogen and progesterone hormones and mild responses might appear which interfere daily activities. Clinical manifestations that can occur are hot flushes, night sweats, insomnia, vaginal dryness, osteoporosis, arteriosclerosis, dyslipidemia, decreased mood, decreased cognitive function, irritability and headache (1, 2). There's quality of life scale called Menopause Rating Scale (MRS) developed in the early '90s that have a function to assess the severity of menopausal complaints in response to a lack of a standard scale to measure the severity of aging symptoms and their impact on quality of life (3).

The severity of these symptoms can be predicted

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by looking at glutathione peroxidase levels, where the lower the glutathione peroxidase level, the higher the intensity of complaints (4). Glutathione peroxidase (GPx) can be used as a marker in determining the severity of menopausal complaints because it has a higher sensitivity and specificity when compared with Menopause Rating Scale (MRS), which from previous studies, has sensitivity and specificity of MRS 70.8 and 73.5% respectively (5). However, GPx has a higher cost when compared with Menopause Rating Scale (MRS) to determine the severity of menopausal complaints. Nevertheless, this study provides a better understanding of menopausal complaints especially in paramedic. A further research about antioxidant supplementation in menopausal women may give us an alternative method to treat menopausal complaints (4).

Cognitive function is generally assessed by Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). This questionnaire consists of 2 versions which is the long version (26 questions) and the short version (16 questions). This questionnaire also has high sensitivity, so it will provide valid results in the case of decreased cognitive function (5, 6).

Hormone Replacement Therapy (HRT) has been shown to reduce symptoms caused by decrease in estrogen during menopausal period. One of the most commonly used HRT is estradiol valerate and norgestrel. The combination of estradiol valerate and norgestrel has been shown to reduce the risk of dementia, osteoporosis and breast cancer (7).

From the background described above, this study's objective is to determine the relationship between administering Estradiol Valerate 2 mg and Norgestrel 0.5 mg with cognitive functions which assessed based on IQCODE in menopausal paramedics at Haji Adam Malik General Hospital Medan.

Method

This study was a quasi-experimental study with pretest-posttest design with the administration of estradiol valerate 2 mg + norgestrel 0.5 mg as intervention. This study was conducted at Haji Adam Malik General Hospital Medan starting from July 2017 to October 2017.

The study population was paramedics who had menopause for at least 12 months and worked at H. Adam Malik General Hospital Medan. The study

subjects were 40 people, selected by consecutive sampling method which met the inclusion and exclusion criteria. Inclusion criteria were as follows: paramedics who are not consuming alcohol, not smoking, not suffering from diabetes and hypertension, not having a history of cancer therapy and a treatment history of organic mental disorders, never undergo hysterectomy and willing to participate in the study. The exclusion criteria were as follows: study subject who withdrew from the study, had improvement and no change IQCODE categories before intervention, and consumed hormone replacement therapy irregularly every month.

To begin the study, the study subjects were asked to fill out informed consent and identity. Then, the study subjects filled the IQCODE questionnaire and were interpreted into increase, no change, a slight decrease, moderate decrease and severe decrease based on IQCODE categories. Furthermore, the study subjects were asked to consume estradiol valerate 2 mg + norgestrel 0.5 mg for 3 months and were followed up every week by telephone. After 3 months, the patient's cognitive function will be evaluated by IQCODE questionnaire.

The data of study subjects were analyzed descriptively and arranged in a frequency distribution table. Inferential analysis is performed to see the difference in IQCODE values before and after the administration of intervention by t-paired test. The results of the analysis are considered significant if the value of $p < 0$.

Results

Out of 40 study subjects, two study subjects were found to have improvement and no change IQCODE categories, and two other subjects were excluded due to tachycardia and loss to follow-up. Therefore, the number of research subjects was 36 people.

The age group of 50-59 years old was the most commonly found age group on the study as many as 26 people (72.2%), followed by the age group 40-49 years (27.8%) and there were no ≥ 60 years old study subject.

A total of 33 people (91.7%) were multiparous, followed by grandmultiparous (8.3%), while none of the study subjects were nulliparous and primiparous. Most of the study subjects were overweight (63.9%), followed by normal (30.6%) and obesity (5.6%).

The study subjects who had experienced menopause for 2 years were 13 people (64.1%), followed by 3 years of menopause (33.3%) and ≥ 4 years (30, 6%) (Table 1).

The most common IQCODE category found before intervention was moderate decline (66.1%), fol-

lowed by slight decline (36.1%) and only 1 person (22.8%) was categorized as severe decline. After the intervention, the most common category found was slight decline (58.3%), followed by improvement (25%), no change (11.1%) and moderate decline (5.6%) (Table 2).

TABLE 1 - STUDY SUBJECTS FREQUENCY DISTRIBUTION BASED ON AGE, PARITY, BODY MASS INDEX AND DURATION OF MENOPAUSE.

Characteristics	Frequency (n)	Percentage (%)
Age (Years)		
40-49	10	27.8
50-59	26	72.2
≥ 60	0	0
Parity		
Nulliparous	0	0
Primiparous	0	0
Multiparous	33	91.7
Grandemultiparous	3	8.3
Body Mass Index		
<i>Underweight</i>	0	0
Normal	11	30.6
<i>Overweight</i>	23	63.9
Obesity	2	5.6
Menopause duration		
2 years	13	36,1
3 years	12	33,3
≥ 4 years	11	30,6
Total	36	100

TABLE 2 - THE FREQUENCY DISTRIBUTION OF STUDY SUBJECTS BASED ON IQCODE CATEGORIES.

IQCODE Categories	Before		After	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
<i>Improvement</i>	0	0	9	25
<i>No change</i>	0	0	4	11,1
<i>Slight decline</i>	13	36,1	21	58,3
<i>Moderate decline</i>	22	61,1	2	5,6
<i>Severe decline</i>	1	2,8	0	0
Total	36	100	36	100

TABLE 3 - THE DIFFERENCE OF IQCODE SCORES BEFORE AND AFTER INTERVENTION.

IQCODE Scores	Mean ± Standard Deviation	P value
Before intervention	3.59 ± 0.26	0.000
After intervention	3.18 ± 0.29	

The mean IQCODE score before intervention was 3.59 ± 0.26 , while the IQCODE score after intervention was 3.18 ± 0.29 with $p = 0.000$ which meant that there was a relationship between the administration of estradiol valerate 2 mg and norgestrel 0.5 mg with the cognitive function. The result showed that there was a decrease in the average IQCODE score or increase in cognitive function after the intervention (Table 3).

Discussion

The process of menopause goes hand in hand with the aging process and is related to the women physical condition and cognitive function. Cognitive function is defined as a person's ability to be able to demonstrate certain abilities, such as learning, memory, visuospatial abilities and executive functions. Cognitive disorders can be classified as a decline in cognitive function along with the aging process, mild cognitive disturbances and dementia. Decrease in cognitive function along with the aging process can be found in women who have underwent menopause and are associated with the inability to carry out daily activities (8).

Based on recent research, shows that sex hormones, especially estrogen and progesterone can affect cognitive function, because both hormones are proven to be one of the factors which causes decreased of cognitive function in menopausal women. Estrogen receptors can be found in the cerebral cortex, hypothalamus, pituitary, limbic system and frontal cortex, cingulate, olfactory, which are the part of the brain that plays a role in cognitive function, memory and mood. Estrogen is believed to trigger neurogenesis in the hippocampus and prefrontal cortex, which is a region that associates with memory and executive function. Therefore, hormonal therapy with estrogen might be a potential strategy in preventing memory loss on the aging process and cognitive impairment in menopausal women with Alzheimer's disease (9).

The results of this study showed that the age group of 50-59 years was the most common age group found on study subjects. According to Kaunitz and Manson's study, menopause occurs in the average age of 51-52 years (10). Most of the study subjects was overweight, followed by normal and obesity. This result is in contrast to the study by Dieny and Fitrianti (2017), which shows that the most common body mass index is obesity (8%) in the age group of 40-50 years, while in the age group 51-60 years, 61-70 years and 71-80 years, the most common body mass index is obesity (11).

The study results showed that most of the study subjects had experienced menopause for 2 years. Based on the results of previous studies, the average length of menopause was 7.23 ± 7.33 years. Different results were found in Wildan's (2012) study, which showed that the 44% of his study subjects had experienced menopause for 6-10 years. This results is obtained from 60-64 years old study subjects. In the postmenopausal phase where the ovaries are not functioning at all, estradiol level is between 20-30 pg /mI and the gonadotropin hormone level usually increases. The increased of gonadotropin hormone is caused by the cessation of inhibin production due to insufficient availability of follicles. Because of the low levels of estradiol, the endometrium becomes atopic and menstruation is no longer possible to happen (12).

The results showed that the most common found IQCODE category before intervention was moderate decline, followed by slight decline and severe decline with 3.59 ± 0.26 as its mean and standard deviation scores. The results of this study are similar to those of Lubis et al. (2017), which showed that 55.8% of the study subjects had moderate decline cognitive function, followed by a slight decline (30.2%) and 2.3% had severe decline cognitive function (2).

During menopause, there is a decrease in estrogen level, thus disrupting the supply of nutrients needed for the development of nerve cells in the brain, so that it tends to cause cognitive impairment, memory,

mood changes and abnormalities in motor coordination. The decreased of estrogen level in a woman's body will cause brain cells to be unable to regenerate, which causes changes in cognitive function such as difficulty in concentrating. In addition, insomnia or sleep disorders can also occur and induce the decrease of quality and quantity of sleep, so that the regeneration of cells in the body cannot be performed, because the body was unable to produce growth hormone. This causes a decrease in concentration and short-term memory function (13, 14).

The results showed that after the intervention the most common IQCODE category found was slight decline, followed by improvement, no change and moderate decline with 3.18 ± 0.29 as its mean and standard deviation scores.

The administration of estrogen (either only estradiol or estradiol and progesterin) can increase antioxidant levels, reduce free radicals and reduce oxidative damage. Estrogen triggers neuron plasticity directly and indirectly. Normal aging process is associated with decreased of dendritic spines and synapses in the dorsolateral prefrontal cortex and hippocampus. Estrogen therapy (ER α and β receptors) can trigger long and thin spine growth in the hippocampus and prefrontal cortex. Presynaptic alpha estrogen receptors are associated with better memory function when treated with exogenous estrogen. Neurotrophin acts as nerve growth factors and brain-derived neurotrophic factor (BDNF) which has plasticity mechanism of other neurons in the brain. By increasing the level of hippocampus BDNF, estrogen can increase the amount of dendritic spines temporarily, which increases neuron plasticity in the brain (15).

Estradiol can protect neurons from ischemic brain

injury. Estrogen interacts with a lot of neurotransmitters that affect cognitive function and mood. On the other hand, natural progesterone has several advantages compared to synthetic progesterone, which is antiandrogenic properties (rarely cause virilization), does not need to be activated first in the liver, and does not decrease HDL levels (16).

Kronos Early Estrogen Prevention Research (KEEPS) states that therapy estrogen and progesterone hormonal therapy has shown to prevent neurodegenerative diseases such as Alzheimer's disease. The results also showed that the group of subjects who received estrogen and progesterone therapy had better results during depression, anxiety and memory examinations. In addition, the combination therapy of oral conjugated equine estrogen 0.625 mg + norgestrel 5 mg for one year can reduce menopausal symptoms, such as hot flush, night sweats, pain in the joints and muscles, insomnia, dry feeling in the vagina so as to improve the quality of life of postmenopausal women. Cognitive function will increase along with the longer consumption combination therapy (17, 18).

Conclusion and recommendations

There is a relationship between the administration of estradiol valerate 2 mg and norgestrel 0.5 mg with cognitive function with p value <0.05 . Some suggestions for further research that might be useful are assessing the effects of hormone therapy with other variables, using different group of study subjects and compares the effect of hormone therapy with the control group.

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