

단기 호르몬 병합 치료가 폐경 후 우울증 환자의 인지 기능에 미치는 영향

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The Effect of Hormone Replacement Therapy for Cognitive Function of Postmenopausal Depression

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ABSTRACT

Purpose : We investigated the effect of menopausal duration on cognitive function using adjunctive hormone replacement therapy(HRT) in postmenopausal women with depression.

Method : Twelve postmenopausal women with depressive disorder were enrolled. Six patients having menopausal duration of less than 3 years was assigned to the short duration group and six patients of more than 3 years to the long duration group. Each patient was treated with conjugated equine estrogen(1.25mg) plus medroxyprogesterone(5mg) for 8 weeks. Cognitive performance was measured by the Verbal Memory Test, Visual Memory Test, Trail Making Test, Digit Symbol Test, and Attention Shift Test. The Beck Depression Inventory was used for evaluation of depressed mood. The reproductive hormone levels were also measured.

Results : The long duration group showed the lower performance only in Trail Making Test B compared with the short duration group at baseline. After 8 weeks, the long duration group performed significantly better in the Trail Making Test B compared with the short duration group. The differences in change of depressive mood and gonadal hormone level between two groups were not significant.

Conclusion : Menopausal duration before HRT may influence the effect of estrogen on cognition in some cognitive domains. This might be related with estrogen receptor hypersensitivity which induced by the longer estrogen deficiency.

KEY WORDS : Menopausal · Depression · Cognitive function · Hormone replacement therapy.

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서론

가

30%

¹⁶⁾

가

¹⁷⁾

가

¹⁸⁾¹⁹⁾

가

Schmidt

²⁾

(gonadotropin)

³⁾

가

2~3

가

(hypothala-

20~30

mus),

(preoptic area),

(ant-

²⁰⁾

가

erior pituitary),

(hippocampus)

3

⁴⁾

3

⁴⁻⁷⁾

가

가

가

연구방법

. Caldwell

⁸⁾

1. 연구대상

45

가

⁹⁻¹¹⁾

가

60

4 (DSM -)

¹²⁾¹³⁾

가

1

가 40

Sherwin

mIU/ml

¹⁴⁾ Kimura,⁹⁾ Schmidt,¹⁰⁾ Jacob ¹¹⁾

4

(Serotonin

selective reuptake inhibitor : SSRI)

3

6

가

¹⁵⁾

12

3

. Gibb

6

가

2. 평가방법

SSRI

(conjugated equine estrogen) 1.25mg

10

(medroxyprogesterone acetate) 5mg

가 (short-term sequential combined hormone replacement therapy) 8

4, 8 가

(Verbal Memory Test),

(Verbal Fluency Test), (Visual Memory Test), (Trail Making Test) A, B, (Digit Symbol Test) (Attention Shift Test)가 4, 8

(Depression Inventory : BDI),²¹⁾ Spielberger state-trait anxiety inventory - State (SAI) Trait (TAI)²²⁾가

(lutealizing hormone : LH), (follicle-stimulating hormone : FSH),

가

, 4, 8

3. 인지평가지도구

Williams Memory Assessment Scale(MAS)²³⁾

Korean Version of Memory Assessment Scale(K-MAS)²⁴⁾ 12

Immediate List Recall() Scale

K-MAS 12

Visual Reproduction Scale

Benton

Oral Fluency Test²⁵⁾

Halstead-Reitan Cattery(HRP)²⁶⁾

, A, B

Wechsler Adult Intelligence Scale - Revised(WAIS-R)²⁷⁾ , 9 1

9

(STIM)

STIM

5가 가 13

가 (Attention switch-

Table 1. Demographic data, baseline psychometric scores, cognitive function test scores and serum hormonal levels of postmenopausal women with depression who were assigned to the short and long menopausal duration group(N=12)

Variables	Short group	Long group	p
	(N=6)	(N=6)	
	Mean ± SD	Mean ± SD	
Baseline characteristics			
Age(years)	50.1 ± 3.6	56.3 ± 6.2	.063
Education(years)	11.0 ± 1.5	11.1 ± 3.3	.182
Menopause duration(years)	1.9 ± 0.4	7.5 ± 3.3	.004*
Measures for psychopathology			
Beck depression inventory	20.8 ± 13.4	24.5 ± 12.4	.688
Status anxiety inventory	39.5 ± 17.3	42.6 ± 12.0	1.000
Trait anxiety inventory	33.8 ± 21.8	42.8 ± 8.6	.229
Measures for cognitive function :			
Verbal memory test	5.3 ± 1.6	5.1 ± 1.4	.806
Visual memory test	5.6 ± 1.3	4.8 ± 1.4	.316
Verbal fluency test	23.1 ± 7.1	17.0 ± 6.48	.078
Trail making test A	47.5 ± 29.2	57.6 ± 19.7	.261
Trail making test B	96.3 ± 64.1	197.1 ± 66.2	.025*
Digit symbol test	47.6 ± 27.7	24.8 ± 3.7	.055
CPTCNC	0.98 ± 0.02	0.93 ± 0.08	.283
CPTCV	0.97 ± 0.02	0.91 ± 0.09	.412
CPTCI	0.84 ± 0.13	0.85 ± 0.14	.872
CPTLN	0.58 ± 0.14	0.44 ± 0.06	.150
CPTLV	0.45 ± 0.12	0.40 ± 0.06	.809
CPTLI	0.48 ± 0.16	0.43 ± 0.11	.522
Hormonal level :			
Prolactin(ng/mL)	8.73 ± 3.20	23.54 ± 24.58	.150
LH(mIU/mL)	47.00 ± 22.69	30.64 ± 11.59	.109
FSH(mIU/mL)	81.65 ± 35.15	72.80 ± 42.99	.337
Estradiol(pg/mL)	34.62 ± 22.56	16.45 ± 8.66	.078
Progesterone (ng/mL)	0.51 ± 0.20	0.38 ± 0.17	.423
Analyzed by Mann-Whitney U test			

ing)

4. 통계분석

SPSS 10.1
0.05

Mann-Whitney U test

연구결과

3.6, 56.3 ± 6.2

(Z = - 1.861, p=0.065).

1.9 ± 0.4, 7.5 ± 3.3

(Z = - 2.913, p=0.04).

(34.62 ± 22.56pg/ml)

(16.45 ± 8.66pg/ml)

(Z = - 1.761, p=.093).

가

4 8

가 , 4

50.1 ±

. 8

(Z = - 2.242, p=.026).

(Z = - 1.844, p=.093)

(1).

4 8

(2).

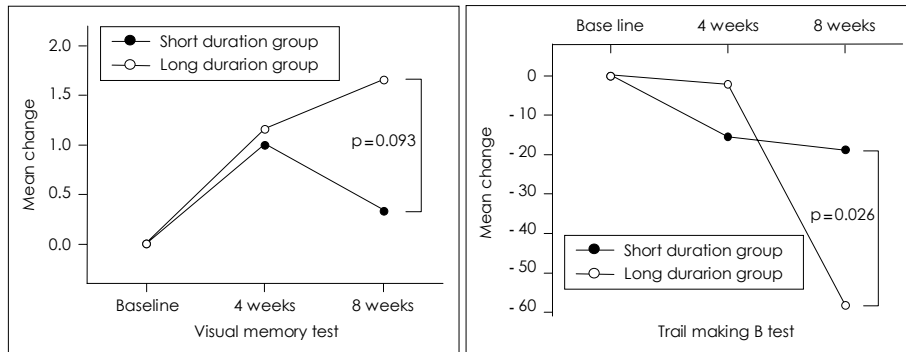


Fig. 1. Comparison of short and long menopausal group for the changes of cognitive function test scores during 8-week hormone replacement therapy.

Table 2. Comparison of the short and long menopause duration groups for the changes in the measure of psychopathology at 4 weeks and 8 weeks from baseline

Measure	4 weeks		p	8 weeks		p
	Short group(N=6) Mean ± SD	Long group(N=6) Mean ± SD		Short group(N=6) Mean ± SD	Long group(N=6) Mean ± SD	
Measure of psychopathology						
BDI	- 8.8 ± 12.0	- 7.0 ± 5.9	1.000	- 10.5 ± 9.8	- 12.5 ± 9.6	.872
SAI	- 11.1 ± 13.4	1.5 ± 12.4	.149	- 7.5 ± 13.7	- 4.6 ± 18.1	1.000
TAI	- 7.8 ± 8.6	- 3.3 ± 3.0	.519	- 6.5 ± 11.3	- 8.3 ± 9.7	1.000

Analyzed by Mann-Whitney U test

Table 3. Comparison of the short and long menopausal group for the hormonal changes at 4 weeks and 8 weeks from baseline

Measures	4 weeks		p	8 weeks		p
	Short group(N=6) Mean ± SD	Long group(N=6) Mean ± SD		Short group(N=6) Mean ± SD	Long group(N=6) Mean ± SD	
Hormonal level :						
Prolactin(ng/mL)	5.14 ± 6.99	- 4.57 ± 13.52	.150	3.96 ± 4.78	8.51 ± 19.73	.873
LH(mIU/mL)	- 30.55 ± 16.04	- 22.68 ± 14.90	.262	- 34.91 ± 20.02	- 24.46 ± 13.35	.262
FSH(mIU/mL)	- 63.71 ± 34.20	- 55.92 ± 45.15	.337	- 65.24 ± 36.62	- 62.54 ± 46.42	.423
Estradiol(pg/mL)	110.61 ± 65.79	74.75 ± 39.09	.200	56.28 ± 77.79	80.27 ± 33.90	.631
Progesterone(ng/mL)	- 0.12 ± 0.33	0.12 ± 0.20	.109	0.07 ± 0.41	0.06 ± 0.52	.423

Analyzed by Mann-Whitney U test

Yolanda 가 Resnick, Hal- reich B B (short - term sequential combined hormone replacement therapy) (estrone) (conjugated equine estrogen) (language) (complex planning) Sherwin Schmidt, Ja- cob, Rice (10)(11)(33) B 가

가 (3). 고 잘 (short - term sequential combined hormone replacement therapy) (estrone) (conjugated equine estrogen) (language) (complex planning) Sherwin Schmidt, Ja- cob, Rice (10)(11)(33) B 가

가 (28 - 31) (36) (37) 가 (38) (29) 가 (39) (conjugated equine estrogen) 1.25mg 10 (medroxyprogesterone acetate) 5mg 가 (short - term sequential combined hormone replacement therapy)

- of estradiol for the treatment of depressive disorders in perimenopausal women: A double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001;58:529-534.
4. Richardson TA, Robinson RD. Menopause and depression: A review of psychologic function and sex steroid neurobiology during the menopause(1). *Prim. Care Update Ob Gyns* 2000;7:215-223.
 5. Rice MM, Graves AB, McCurry SM, Larson EB. Estrogen replacement therapy and cognitive function in postmenopausal women without dementia. *Am J Med* 1997;103:26S-35S.
 6. Luine VN, Khylichevskaya RI, McEwen BS. Effect of gonadal steroids on activities of monoamine oxidase and choline acetylase in rat brain. *Brain Res* 1975;86:293-306.
 7. Gazzaley AH, Weiland NG, McEwen BS, Morrison JH. Differential regulation of nmdar1 mRNA and protein by estradiol in the rat hippocampus. *J Neurosci* 1996;16:6830-6838.
 8. Caldwell BM, Watson RI. An evaluation of psychologic effects of sex hormone administration in aged women. I. Results of therapy after six months. *J Gerontol* 1952;7:228-244.
 9. Kimura D. Estrogen replacement therapy may protect against intellectual decline in postmenopausal women. *Horm Behav* 1995;29:312-321.
 10. Schmidt R, Fazekas F, Reinhart B, Kapeller P, Fazekas G, Offenbacher H, et al. Estrogen replacement therapy in older women: A neuropsychological and brain MRI study. *J Am Geriatr Soc* 1996;44:1307-1313.
 11. Jacobs DM, Tang MX, Stern Y, Sano M, Marder K, Bell KL, et al. Cognitive function in nondemented older women who took estrogen after menopause. *Neurology* 1998;50:368-373.
 12. Polo-Kantola P, Portin R, Polo O, Helenius H, Irjala K, Erkkola R. The effect of short-term estrogen replacement therapy on cognition: A randomized, double-blind, cross-over trial in postmenopausal women. *Obstet Gynecol* 1998;91:459-466.
 13. Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: The women's health initiative memory study: A randomized controlled trial. *JAMA* 2003;289:2663-2672.
 14. Sherwin BB. Estrogen and/or androgen replacement therapy and cognitive functioning in surgically menopausal women. *Psychoneuroendocrinology* 1988;13:345-357.
 15. Zec RF, Trivedi MA. The effects of estrogen replacement therapy on neuropsychological functioning in postmenopausal women with and without dementia: A critical and theoretical review. *Neuropsychol Rev* 2002;12:65-109.
 16. Gibbs RB. Long-term treatment with estrogen and progesterone enhances acquisition of a spatial memory task by ovariectomized aged rats. *Neurobiol Aging* 2000;21:107-116.
 17. Lacreuse A, Wilson ME, Herndon JG. Estradiol, but not raloxifene, improves aspects of spatial working memory in aged ovariectomized rhesus monkeys. *Neurobiol Aging* 2002;23:589-600.
 18. Matthews K, Cauley J, Yaffe K, Zmuda JM. Estrogen replacement therapy and cognitive decline in older community women. *J Am Geriatr Soc* 1999;47:518-523.
 19. Marder K, Sano M. Estrogen to treat Alzheimer's disease: Too little, too late? So what's a woman to do? *Neurology* 2000;54:2035-2037.
 20. Malcolm Whitehead VG. Hormone replacement therapy: Your questions answered. 1. Edinburgh London Madrid Melbourne New York and Tokyo. Churchill Livingstone; 1992. p.7-10
 21. Beck AT. Depression: Clinical, experimental, and theoretical aspects. New York. Harper;1976.
 22. Spielberger C. State trait anxiety inventory test (stai). North Tonawanda, NY. MHS, Inc;1983.
 23. Williams JM. Memory assessment scales professional manual psychological assessment resources. Odessa, FL; 1991.
 24. Lee HS, Park BK, Ann CI, Kim Mh, Jung IK. Korean version of memory assessment scale. Seoul, Korea. Korea Guidance;2001.
 25. Benton AL. Differential behavior effects in frontal lobe disease. *Neuropsychologia* 1968;6:53-57.
 26. Reitan RM WD. The halstead-reitan neuropsychology test battery: Theory and clinical interpretation. Tucson, AZ. Neuropsychology Press;1985.
 27. Wechsler D. Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R). San Antonio. The Psychological Corporation;1981.
 28. Phillips SM, Sherwin BB. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;17:485-495.
 29. Kampen DL, Sherwin BB. Estrogen use and verbal memory in healthy postmenopausal women. *Obstet Gynecol* 1994;83:979-983.
 30. Smith YR GB, Lakiness-O'Neil R, Zubieta JK. Long-term estrogen replacement is associated with improved nonverbal memory and attentional measures in postmenopausal women. *fertility and sterility* 2001;76:1101-1107.
 31. Resnick SM ME, Zonderman AB. Estrogen replacement therapy and longitudinal decline in visual memory. A possible protective effect? *Neurology* 1997;49:1491-1497.
 32. Thompson K, Sergejew A, Kulkarni J. Estrogen affects cognition in women with psychosis. *Psychiatry Res* 2000; 94:201-209.
 33. Rice MM GA, McCurry SM, Gibbons LE, Bowen JD, McCormick WC, Larson EB. Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive

- change in a cohort of older japanese american women. *Arch Intern med* 2000;160:1641-1649.
34. Halbreich U, Lumley LA, Palter S, Manning C, Gengo F, Joe SH. Possible acceleration of age effects on cognition following menopause. *J Psychiatr Res* 1995;29:153-163.
 35. Morse CA RK. Memory after menopause: Preliminary considerations of hormone influence on cognitive function. *Arch Womens Ment Health* 2005;8:155-162.
 36. Sherwin BB. Estrogen and cognitive functioning in women. *Endocr Rev* 2003;24:133-151.
 37. Shaywitz SE, Shaywitz BA, Pugh KR, Fulbright RK, Skudlarski P, Mencl WE, et al. Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *JAMA* 1999;281:1197-1202.
 38. Rice MM, Graves AB, McCurry SM, Gibbons LE, Bowen JD, McCormick WC, et al. Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive change in a cohort of older japanese american women: The kame project. *Arch Intern Med* 2000;160:1641-1649.
 39. Drake EB, Henderson VW, Stanczyk FZ, McCleary CA, Brown WS, Smith CA, et al. Associations between circulating sex steroid hormones and cognition in normal elderly women. *Neurology* 2000;54:599-603.
 40. Sherwin BB. Estrogen and memory in women: How can we reconcile the findings? *Horm Behav* 2005;47:371-375.
 41. Smith YR, Giordani B, Lajiness-O'Neill R, Zubieta JK. Long-term estrogen replacement is associated with improved nonverbal memory and attentional measures in postmenopausal women. *Fertil Steril* 2001;76:1101-1107.
 42. Martin LA, Farmer I, Johnston SR, Ali S, Dowsett M. Elevated erk1/erk2/estrogen receptor cross-talk enhances estrogen-mediated signaling during long-term estrogen deprivation. *Endocr Relat Cancer* 2005;12 Suppl 1:S75-84.
 43. Klaiber EL, Broverman DM, Vogel W, Peterson LG, Snyder MB. Relationships of serum estradiol levels, menopausal duration, and mood during hormonal replacement therapy. *Psychoneuroendocrinology* 1997;22:549-558.