

Original Article

Effect of Hormone Replacement Therapy on Memory in Post Menopausal Women

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ABSTRACT

Objectives: To study the differential effects of estrogen and progestin on memory in postmenopausal women receiving hormone replacement therapy (HRT). **Methods:** Thirty women between ages 45 and 60 years who had attained natural menopause and received combined estrogen progestin therapy constituted group I. While group II included 30 surgically menopausal women who received only estrogen, PGI memory scale having a battery of ten subtests devised specially for Indian subjects was used. Results were analyzed by repetitive measure analysis. **Results:** Women showed an improved score on memory scale after 6 months of HRT in both the groups. The comparison of both groups post therapy revealed improvement in scores of delayed recall & visual retention in group II indicating that only estrogen users benefited more. **Conclusion:** This study supports the view that estrogens with or without progestin if given early after menopause i.e. below 60 yrs if age do have a beneficial role on memory.

Key Words: Postmenopausal women, Hormone replacement therapy, Memory.

Introduction

Menopause in women occurs at the mean age of 48.5 ± 4 years and is marked by the cessation of ovulation and a dramatic decline in the production of ovarian hormones. The decline in circulating estradiol after menopause has significant effects on the functioning of CNS as evidenced by change in behavior and there is a growing body of literature documenting the beneficial effect of estrogen on mood and cognition.¹⁻³ The electrophysiology cal evidence suggesting improvement in sensory function is also reported.⁴ Estrogens alone can safely be used in women who have had a hysterectomy done while for all other women the addition of progestin is required in order to prevent estrogen associated endometrial and breast cancer.

In postmenopausal HRT progestins are generally felt to have a negative or attenuating effect on the improved global scores of well being attained with estrogen alone.^{5,6} Progestin has been found to be associated with negative mood changes both during the menstrual cycle and in women taking oral contraceptives.⁷ Whether this dampening effect

of progestins on mood also reflects in a negative effect on memory is not much studied. Memory loss is prominent among the complaints of postmenopausal women as indicated by various studies.^{8,9} This paper focuses on studying the differential effects of the estrogens and progestins on memory.

The memory scale used in the present study is devised specially for Indian subjects. It is equally applicable and acceptable to subjects from low socio-economic strata, which constitute majority in Indian government hospitals.

Material and methods

Subjects

Sixty postmenopausal women between ages 45 and 60 years attending Menopause and Hormone Replacement Therapy Clinic of University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi were selected over a period of eighteen months. The subjects attending HRT clinic for postmenopausal symptoms only were selected for the study. The average education level of the subject studied was up till class V. Broadly, these

females were divided into two groups.

Group I: It included 30 women who had attained natural menopause (without surgical removal of ovaries) for at least one year. Mean age of the subjects being 54.8 ± 3.8 years. They were administered a continuous sequential regimen, which consisted of estrogen in form of conjugated equine estrogen 0.625 mg given daily throughout the month, and progestin as dydrogesterone 10mg daily for 1-12 days of each calendar month.

Group II: It included 30 surgically menopausal women i.e. women who had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy who received only estrogen. Mean age being 49.6 ± 3.5 .

Both the above therapies were given for at least 6 months. The two groups were matched for age, level of education and postmenopausal period. Except for postmenopausal symptoms like hot flushes, night sweats, insomnia and mood swings, these patients were not suffering from any medical ailments.

Exclusion criteria were

- Women having depressive disorder of any other psychiatric illness.
- History of head injury, stroke, heart attack or alcoholism
- Women having breast cancer at any time or suspicion of breast cancer
- Known chronic hepatitis or severe cirrhosis
- Women on any medication

Memory tests were done before starting a course of hormone replacement therapy (these served as control values) and repeated after six months of administration of HRT. Informed consent was taken from the subjects and the institute's ethical committee approved the study.

A battery of investigations, which included serum estradiol, lipid profile, blood sugar, mammography and Pap smear, were performed on patients before starting HRT.

Tools

PGI memory scale¹⁰ having a battery of ten subtests devised specially for Indian subjects was used. It is equally applicable and acceptable to subjects belonging to low socioeconomic strata, which constitute majority in Indian government hospitals.

Procedure

The subjects were explained about the test and were relaxed. The tests were done as per the instructions of PGI memory scale¹⁰ and scoring was done simultaneously in the following order.

1. **Remote memory:** Some common questions of their past were asked like where were they born? When did they get married? What is the age of their youngest child or brother or sister? When did they come to the hospital for the first time? etc. A score of one was given for each correct response. Maximum score was 6.
2. **Recent memory:** Questions relevant to the recent past were asked and scored accordingly. e.g. what did you eat last night? Which month is this? Whom did you meet yesterday? etc. A score of one was given for each correct response. Maximum score was 5.
3. **Mental Balance:** In the first part the subjects were asked to speak out the alphabets i.e. from A to Z. Next they were asked to count numbers in the reverse order i.e. from 20 to 0. For both alphabets and counting backwards, the score is 3 if all correct within 15 seconds, 2 if they take longer than 15 seconds, score of 1 if there is one mistake or omission separately for alphabet and backward counting. In the third part of the test the subjects were asked to count backwards from 40 by subtracting 3 from each number. In this counting backwards by 3's-3 scores if all correct within 30 seconds, 2 if she takes longer than 30 seconds, 1 if there is one error or omission.
4. **Attention and concentration:** Few numbers were spoken out and subjects were asked to repeat them in the same order and then in the reverse order e.g.: 5-7-3, 5-3-8-7, 1-6-4-9-5. These digits were presented in an increasing order, till the subjects were unable to repeat them correctly. Summation of digits forward and backward is the score of the subtest.
5. **Delayed Recall:** This test assesses storage, retention and retrieval of spoken words. Ten unrelated words are read to the subject at a rate of one word per second. The subjects are asked to recall the entire list after an interval of one minute. A score of one is given for each word correctly recalled. Maximum score is 10.

6. **Immediate Recall:** It assesses verbal memory for prose material. A group of 3,4 or 5 clauses were spoken and the subjects were asked to repeat them. A score of one for each clause correctly reproduced Maximum score 12.
7. **Verbal retention for similar pair:** Pair of associated words was read out at a speed of 2 per second with an interval of 5 seconds in between e.g.: tree-flower, day-night, man-woman etc. After an interval of ten seconds the subjects were given the first word and asked to reproduce the associated word of the pair. Maximum score is 5.
8. **Verbal retention for dissimilar pairs:** A pair of dissimilar words is read out to the subjects. After an Interval of 10 seconds, the subjects were given the first word and asked to indicate the word with which it was paired. Three trials were given. A score of one for each correctly reproduced pair separately for each trial. Maximum score is 15.
9. **Visual retention:** Adapted from Wechsler's memory scale to assess memory from visualization of geometric forms. Various cards with geometric figures were shown one after another to the subjects for 15 seconds. After an interval of 30 seconds, subjects were asked to draw the geometric form on a paper. A score of one for each type of figure correctly reproduced in sequence and number. Maximum score is 12.
10. **Recognition:** A card having few pictures was shown to the subject for 30 seconds. Then after an interval of 2 minutes another card having more pictures were shown and the subject was asked to point out (recognize) the pictures shown in the previous card. Each picture correctly recognized and named is to be given a score of one. Number of wrong identified picture is to be deduced from the earned score. Maximum score is 10.

Statistics

All statistical analysis was carried out using SPSS 10.0 statistical package. Repetitive measure analysis (ANOVA) design was done with Tukey test and 5% level of significance.

Results

In group I (estrogen + progestin users) the scores in mental balance, attention concentration, delayed recall and immediate recall had improved significantly after 6 months of administering HRT (Table 1). While remote memory, recent memory, retention for similar pairs, retention for dissimilar pairs, visual retention and recognition did not show a significant change.

Table-1 Memory scores before and after HRT in the two groups

S. No.	Tests	Max Score	Group I n=30		Group II n=30	
			Before HRT	After HRT	Before HRT	After HRT
1.	Remote memory	6	4.81 ± 0.93	4.91 ± 0.78	4.80 ± 0.86	5 ± 0.65
2.	Recent memory	5	3.94 ± 0.84	3.97 ± 0.82	4.07 ± 0.88	3.87 ± 0.92
3.	Mental balance	9	4 ± 1.55	5.97 ± 1.18*	3.80 ± 1.93	6.47 ± 0.83*
4.	Attention & Concentration	10	7.03 ± 1.80	8.81 ± 1.86*	7.27 ± 2.31	9.67 ± 1.40*
5.	Delayed recall	10	5.94 ± 1.19	7.37 ± 1.48*	6.07 ± 1.28	8.20 ± 1.21*
6.	Immediate recall	12	3.31 ± 1.06	6.34 ± 1.68*	4.27 ± 1.16	6 ± 2.04*
7.	Verbal retention for similar pairs	5	4 ± 0.92	3.94 ± 0.88	3.73 ± 1.03	3.80 ± 1.01
8.	Verbal retention for dissimilar pairs	15	3.97 ± 0.86	4.47 ± 1.67	4.13 ± 0.83	4.27 ± 1.62
9.	Visual retention	12	2.06 ± 1.46	3.78 ± 1.60	3.07 ± 1.62	4.20 ± 1.61*
10.	Visual recognition	10	8 ± 1.02	8.22 ± 1.01	8.20 ± 1.21	8.13 ± 1.25

*P < 0.05

All the values are scores hence on units.

In group II (only estrogen users) there was a significant improvement in scores of mental balance, attention concentration, delayed recall, immediate recall and visual retention after HRT.

While comparing the two groups post therapy with HRT (Table 2), it was noted that group II (estrogen users) showed significant improvement in scores of delayed recall and visual retention as compared to group I (estrogen + progestin users).

for this test not coming significant. Similar effects of estrogen on cognition, mood and memory are also reported.^{8,9,14} In contrast, no effect of memory, for verbal information (Logical memory) is observed by others.⁷ One possible explanation for the inconsistency among studies may be the use of verbal memory tasks that vary in the extent to which they recruit frontal lobe functions.

The present study has also studied the effect

Table 2: Post therapy scores compared in the two groups

S.No.	Tests	Max Score	Group I n=30	Group II n=30
1.	Remote memory	6	4.91 ± 0.78	5 ± 0.65
2.	Recent memory	5	3.97 ± 0.82	3.87 ± 0.92
3.	Mental balance	9	5.97 ± 1.18	6.47 ± 0.83
4.	Attention & Concentration	10	8.81 ± 1.86	9.67 ± 1.40
5.	Delayed recall	10	7.37 ± 1.48	8.20 ± 1.21*
6.	Immediate recall	12	6.34 ± 1.68	6 ± 2.04
7.	Verbal retention for similar pairs	5	3.94 ± 0.88	3.80 ± 1.01
8.	Verbal retention for dissimilar pairs	15	4.47 ± 1.67	4.27 ± 1.62
9.	Visual retention	12	3.78 ± 1.60	4.20 ± 1.61*
10.	Visual recognition	10	8.22 ± 1.01	8.13 ± 1.25

*P < 0.05

All the values are scores hence on units.

Discussion

In the present study, we have observed that postmenopausal women tested while taking estrogen and progestin (group I) or estrogen alone (group II) for six months had a better score on memory scale as compared to their scores before starting therapy.

Several studies have looked at the effect of estrogen on cognitive function in healthy postmenopausal women. The results of these studies have been conflicting which most likely reflects methodological differences but the majority shows that the estrogen improves some memory functions and verbal memory in particular.¹¹⁻¹³ The present study has also shown significant improvement in some aspects of verbal memory i.e. delayed and immediate recall, which are a type of word recall and paragraph recall. While the verbal retention for similar and dissimilar pairs were not significant in the present study. The scores of test 7 (Verbal retention for similar pairs) was already high before starting therapy and there was very little scope for improvement in it. This may be one of the reasons

of estrogen on non-verbal tasks. It was observed that there was a significant improvement in mental balance, attention concentration and visual retention, after 6 months of estrogen therapy. Similar results are observed in other studies also.^{11,12} Thus, there is evidence that estrogen affects not only verbal but also nonverbal aspects of cognitive function in healthy post-menopausal women. In our study although scores of visual retention had improved after HRT, the overall scoring was very low in this test in both the groups. Which may be due to the low education level of the subjects selected, hence they were not able to reproduce geometric forms accurately.

In post menopausal HRT progestin is generally felt to have a negative or attenuating effect on the improved global scores of well being attained with estrogen alone.^{5,6} In the present study there was improvement in memory scores in both the groups, but on comparing the two groups post therapy group II (only estrogen users) showed improvement in scores of delayed recall and visual retention, indicating that only estrogen users are benefited

more as compared to women using combined estrogen progestin therapy. Similar findings were observed in a clinical study where conjugated equine estrogen alone showed good changes of cognitive tests for Alzheimer's disease, but addition of progestin suppressed these tests.

Various HRT trials in non-demented postmenopausal women suggest a temporary positive effect on memory and a possible protective effect in relation to Alzheimer's disease.^{6,13} However, data from the only large randomized controlled trial published to date, the women's health initiative memory study (WHIMS),¹⁵ did not confirm these observations and even suggested as increase in dementia risk for women using HRT compared to controls. WHIMS answered critically important questions about whether HRT can protect against dementia in elderly women who start HRT some years after menopause. However, several clinically important questions are unanswered, including questions about the generalisability of the WHIMS to groups of women for whom HRT is an indication like perimenopausal women and those soon after menopause who have menopausal symptoms, and other methods of treatment delivery and treatment regimens. More over this trial was done on women above 65 years of age, while in the present study all the subjects were below 60 yrs of age and none of them were suffering from dementia as such.

Conclusions

This study supports the view that estrogens with or without progestins if given early after menopause i.e. below 60 yrs of age and when the neurons are in a healthy state do have a beneficial role on memory. Moreover only estrogen users are benefited more as compared to women using combined estrogen progestin therapy.

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