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# DIFFERENTIAL EFFECTS OF EXOGENOUS ESTROGEN VERSUS A ESTROGEN–PROGESTERONE COMBINATION ON AUDITORY EVOKED POTENTIALS IN MENOPAUSAL WOMEN

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**Abstract :** The study was undertaken *to* determine the differential effects of estrogen and progestin on auditory evoked responses in postmenopausal women receiving hormone replacement therapy (HRT). Forty-seven women between 45 and 70 years of age attending menopause and HRT clinic were divided into two groups. Group I included 32 women who attained natural menopause and receiving combined estrogen progestin therapy. While group II included 15 surgically menopausal women receiving only estrogen. Evoked potentials were recorded in form of auditory brainstem response (ABR), middle latency response (MLR) & slow vertex response (SVR). There was improvement of conduction in auditory pathways at the level of brainstem and thalamocortical projections as indicated by the decrease in latencies of most of the waves of ABR and/ MLR after 6 months of HRT in both the groups. The conduction in association areas, as indicated by SVR, did not show a significant change. The intergroup comparison after therapy revealed a decrease in latency of wave V and I-V interpeak latency in group II indicating that only estrogen users are benefited more. Thus HRT facilitates the process of sensory conduction, which may form one of the mechanisms of improved neuropsychological functions in menopausal women on HRT. The addition of progestin to estrogen does not have a negative or potentiating effect on it.

**Key words :** postmenopausal women estrogen progestin hormone replacement therapy auditory brainstem response (ABR) middle latency response (MLR) slow vertex response (SVR)

## INTRODUCTION

The menopause constitutes a watershed in a woman's life that leads to profound changes in several systems. As the realization of the multisystem nature of these changes ranging from psychological (brain) to osteoporosis in bone and cardiovascular changes has developed, also has the awareness that many of these changes can be prevented or completely modified with hormone replacement therapy (1).

Women live about one third of their lives

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beyond cessation of their reproductive capacity. Hence it becomes a challenge to medical scientists and physicians to prevent or retard, not only the physically disabling degenerative changes but also the neuropsychological ones so as to enhance their quality of life during the latter third of their lifespan. To this end it is important to elucidate the psycho-physiological effects of estrogen and progestin and their mechanism of action.

In most psycho physiological assessments, evoked potential responses (EPR) are considered to be a useful adjunct. However these have not been studied adequately in the menopausal females. Hence we had earlier conducted a study of EPR in normal menopausal females and found significant deviations of EPR latencies from the normal (2). The EPR's in menopausal women on combined estrogen progestin therapy was also studied by us (3) and a significant improvement of conduction in auditory pathway was observed. A hormonal hypothesis was proposed to account for the above changes. In addition to auditory brainstem response (ABR obtained within 0–5 ms of application of the stimulus), the middle latency response (MLR between 8–50 ms) & slow vertex response (SVR more than 50 ms) were also studied to assess the entire auditory pathway from auditory nerve to auditory cortex and association areas.

As an extension of our earlier work we have now evaluated separately the effects of estrogen and progestin on auditory evoked responses.. In postmenopausal HRT progesterones are generally felt to have a negative or attenuating effect on the improved global scores of well being attained with estrogen alone (4–7). In the present study we intend to extract inferences regarding the differential effects of two hormones on auditory evoked responses.

## MATERIALS AND METHODS

**Subjects :**

Forty-seven postmenopausal women between 45 & 70 years of age attending Menopause and Hormone Replacement Therapy clinic of UCMS & GTB Hospital Delhi were selected over a period of eighteen months. The mean education of subjects were class V. Broadly these females were divided into two groups

Group I : Thirty-two women who had attained natural menopause (without surgical removal of ovaries) for at least one year after the age of 40 yrs. They were given a continuous sequential regimen, which consisted of estrogen as conjugated equine estrogen (CEE) 0.625 mg daily throughout the month, and progestin as dydrogesterone 10 mg daily for 1–12 days of each calendar month.

Group II : Fifteen surgically menopausal women i.e. women who had undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy and were receiving only conjugated equine estrogen 0.625 mg.

Except for postmenopausal vasomotor symptoms like hot flushes and night sweats, these patients were not suffering from any medical ailments. Exclusion criteria were

– Women receiving drug therapy or psychotherapy for depression.

– History of head injury, stroke, heart attack or alcoholism

– Hearing threshold more than 40 dB

Recordings were done before starting a course of hormone replacement therapy (the control values) and after six months of HRT. Post therapy recordings were done between 5th to 8th day of the cycle in group I and anywhere in the cycle for group II. Informed consent was taken from the subjects and institutes ethical committee approved the study.

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

**Tools :**

For evoked potentials: Computerized evoked potential recording equipment model MEB 5200 (Nihon Kohden, Japan) with Ag/AgCl disc electrodes was used.

**Procedure :**

The subjects were lying down and relaxed at the time of testing in soundproof air-conditioned room. EPR's were obtained from Ag/AgCl disc electrodes affixed with collodion at 10/20 international placement (8). Positive electrode was kept at Cz position, negative (reference) at ipsilateral ear lobule ($A_1$) and the ground electrode at the forehead. The contact impedance was constantly monitored with an impedance meter and electrode to skin contact resistance was kept below 5 k ohm. Alternating clicks at the rate of 10/sec were delivered at 90 dB through shielded earphones with-40 dB pure white noise masking of the contralateral ear. For ABR this was then filtered (with band pass 150–3000 Hz) and averaged to 2048 stimuli. Recordings were obtained from each ear separately in duplicate. The absolute peak latency, interpeak latency and amplitude of waves were measured with cursors on the screen. For MLR 256 clicks were given at alternate polarity for 0.1 ms at the rate of 5/sec, at intensity of 90 dB. SVR was measured by giving 64 clicks of alternate polarity for 0.1 ms at the rate of 0.5/sec and at same sound intensity.

**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

The evoked potential recordings were analyzed separately for each ear of all the subjects and therefore the recordings were obtained from 64 (32 × 2) ears of group I and from 30 (15 × 2) ears of group II women.

*ABR (Table I and II).*

In group I patients (on estrogen

TABLE I: ABR latencies in menopausal women on HRT.

| | | No. of ears tested (n) | Latencies (m sec) | | | | | Interpeak latancies (m sec) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | I | II | III | IV | V | I-III | I-V | III-V |
| Group I | Before HRT | 64 | 1.67±0.13 | 2.71±0.14 | 3.88±0.22 | 5.16±0.46 | 5.85±0.28 | 2.20±0.27 | 4.17±0.29 | 2.33±0.38 |
| | After HRT | 64 | 1.49±0.02* | 2.56±0.43 | 3.59±0.22* | 4.85±0.32* | 5.61±0.30* | 2.10±0.23 | 3.86±0.39* | 1.96±0.29* |
| Group II | Before HRT | 30 | 1.70±0.1 | 2.72±0.13 | 3.92±0.39 | 5.06±0.35 | 5.82±0.25 | 2.21±0.37 | 4.11±0.16 | 1.89±0.36 |
| | After HRT | 30 | 1.47±0.02* | 2.57±0.02 | 3.61±0.02* | 4.79±0.11* | 5.53±0.16* | 2.13±0.11 | 4.05±0.19* | 1.82±0.15 |

*P<0.05.

TABLE II: ABR Amplitude (mV) in menopausal women on HRT.

| | | No. of ears tested (n) | Amplitude in mV | | |
|---|---|---|---|---|---|
| | | | I | III | V |
| Group I | Before HRT | 64 | 0.33±0.02 | 0.35±0.02 | 0.37±0.03 |
| | After HRT | 64 | 0.36±0.01* | 0.36±0.03 | 0.41±0.02* |
| Group II | Before HRT | 30 | 0.33±0.02 | 0.35±0.02 | 0.38±0.02 |
| | After HRT | 30 | 0.36±0.02* | 0.37±0.02* | 0.40±0.02* |

*P<0.05.

TABLE III: MLR latencies (m sec) in menopausal women on HRT.

| | | No. of ears tested (n) | No | Po | Na | Pa | Nb |
|---|---|---|---|---|---|---|---|
| Group I | Before HRT | 64 | 9.96±0.35 | 14.09±0.52 | 17.25±0.45 | 24.81±0.46 | 38.09±0.99 |
| | After HRT | 64 | 9.82±0.67 | 13.15±0.49* | 16.25±0.48* | 20.41±0.75* | 37.51±1.05 |
| Group II | Before HRT | 30 | 9.88±0.43 | 14.17±0.61 | 17.25±0.56 | 24.87±0.32 | 37.81±1.04 |
| | After HRT | 30 | 9.61±0.82 | 13.30±0.53* | 16.44±0.61* | 19.98±0.45* | 36.68±1.09* |

*P<0.05.

progesterone combination therapy) the ABR latencies of waves I, III, IV and V and interpeak latencies I-V and III-V were significantly decreased (P<0.05) after 6 months of HRT (Table I), while the amplitude of waves I and V (Table II) were significantly increased as compared to the recordings taken before starting HRT (P<0.05). Similar findings were observed in group II patients (only estrogen therapy) i.e. ABR latencies of waves I, III, IV, V and interpeak latencies of I-V significantly decreased & amplitudes of wave I, III and V significantly increased after 6 months of therapy. The two groups when compared after their respective HRT's revealed a significant decrease in latency of wave V & l-V interpeak latency in group II.

*MLR (Table III)*

In group I, MLR latencies of waves Po, Na and Pa were significantly less (P<0.05)

after HRT. The latencies of waves No and Nb were also decreased after HRT but the values could not reach the level of significance. Similar findings were observed in group II, with an additional significantly decreased latency of Nb. The groups when compared after their respective HRT's revealed no significant difference in MLR waves.

**SVR :**

In both group I and II the trend is towards a decrease in latency of all the waves after HRT but it could not reach the level of significance.

There was no significant difference in the recordings between the two ears of a subject.

## DISCUSSION

The present study shows the improvement in the conduction of the auditory pathways after six months of HRT in both the groups (estrogen + progesterone and estrogen alone). The conduction was significantly improved at the level of brain stem up to the auditory cortex as indicated by the decrease in latencies of most of the waves of ABR and MLR and also a decrease in interpeak latencies of ABR waves. While the auditory association areas as indicated by SVR did not show a significant change. Caruso et al (9) have also shown similar results for ABR's in postmenopausal women treated with HRT. In their HRT group the ABR wave latencies and interpeak latencies were shorter than those from women not taking HRT overlapping those of the premenopausal women. This is in agreement., with the suggestions made by Rosenhamer (10) for the possible influence of the hormonal factor on sensory conduction. This view was further strengthened by others (11–16).

In our previous study, the combined (estrogen + progestin) hormonal therapy for 6 months resulted in a decrease in most of the latencies and interpeak latencies of ABR (3). These parameters were earlier reported by us to be increased in menopausal females as compared to young adult females pointing towards a delayed neural transmission due to a changed hormonal milieu of sex hormones after menopause (2). The sex hormones were proposed to be responsible for increase in auditory conduction.

The present study did not show much difference in the values of auditory evoked potentials between the two groups (estrogen + progestin as compared to estrogen users alone). Although the two after treatment groups when compared revealed a decrease in latency of wave V and I-V interpeak latency in group II (only estrogen users) for ABR, while MLR and SVR did not show a significant change. Similar findings on ABR were also reported earlier (9). Slightly better results of Gp II (only estrogen users) can be explained on the basis of earlier reports (17, 18) that there are interactions between estrogen and acetylcholine for improvement of sensory transmission and the possibility of acetylcholine as one of the neurotransmitters in auditory pathway (19). Estrogen is known to directly influence neurochemical transmitter systems affected in normal aging Alzheimer's disease and other neuropsychiatric disorders. For example

estrogens can modulate the serotonergic, cholenergic and dopaminergic systems (20, 21). In addition to direct effects on neurons, estrogens also work with neurotrophins (such as nerve growth factor) to stimulate indirectly nerve cell growth (22). Estrogen also has a neuroprotective action (23) against several toxins that boost production of free radicals, including glutamate (which is toxic in high concentrations) and beta amyloid.

In post menopausal HRT progestins are generally felt to have a negative or attenuating effect on the improved global scores of well being attained with estrogen alone (4–7). But the present study has not shown much difference in the two groups indicating that progesterone is neither opposing nor potenciating the effects of estrogen as far as auditory conduction is concerned.

As per Voigt and others (24) estrogen users incur a risk of endometrial cancer three times that of non-users with unopposed estrogen use. In one study (25) the incidence of endometrial hyperplasia was considerably lower in a group given transdermal estradiol plus cyclic progestin than in a group of women given unopposed transdermal estradiol. In the present study unopposed estrogen was given to only those women who had hysterectomy done and therefore this side effect of estrogen was excluded.

In middle latency response (MLR) the latencies of waves Po, Na & Pa decreased significantly after HRT in both the groups in the present study again indicating that progestin is not influencing the effects of estrogen in the central auditory conduction as well. It was reported earlier that the latencies of most of the waves of MLR were significantly lower in young adult females as compared to males. But this difference disappeared in elderly subject's (26). This was not due to smaller size of brain in women and hence a shorter neural transmission pathway because the difference disappeared at a later age. This could also not be explained on the basis of marked cerebral involution in elderly women. Since electrophysiological studies demonstrated a predominance of low rhythms (relative delta activity) in elderly men, whereas in elderly women, the relative beta activity prevailed, an index of a more marked aging process in male's (27). Hence the hormonal hypothesis again stands true for MLR's since their latencies are observed to be significantly improved in women on HRT of both the groups.

In the SVR there was no significant difference obtained on HRT in the present study. This can be explained as these components have widespread distribution over the fronto-parietal scalp area (28) and it is difficult to pick them up by a single active electrode. Even if they are located precisely, they do vary with certain factors like sleep and level of alertness (29). Hence MLR's are a more sensitive indicators of conduction in higher auditory pathways. Literature is deficient in the data of MLR and SVR in menopausal women taking HRT, but since these are exploring a wider tract of auditory pathway i.e. temporoparietal association cortex up to the frontal cortex is a more complete and appropriate method than ABR alone for testing the sensory auditory pathways.

**Conclusion :** The present study reveals the improvement of conduction in auditory pathways at the level of brainstem and thalamocortical projections as indicated by the decrease in latencies of most of the waves of ABR and MLR after 6 months of HRT in both the groups. The conduction in association areas, as indicated by SVR, did not show a significant change. The intergroup comparison after therapy revealed a decrease in latency of wave V and I-V interpeak latency in group II, indicating that only estrogen users are benefited more. Thus HRT facilitates the process of sensory conduction, which may form one of the mechanisms of improved neuropsychological functions in menopausal women on HRT. The addition of progestin to estrogen does not have a negative effect on it.

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