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Effect of Tamoxifen on Visual Pathway of Human and Wistar Rat using Visual Evoked Potential

KEYWORDS: Tamoxifen, visual pathway, visual evoked potential, Breast cancer.

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ABSTRACT *Aim: Tamoxifen is a drug which is used for treatment of breast cancer. Beside its advantages for breast cancer treatment, it has certain side effects. The aim of present study is to search for its side effects on visual pathway both in human and animal groups using visual evoked potential.*

Method: Twenty five female patients with tamoxifen treatment for breast cancer were selected for the purpose of recent work. Along with human population twenty wistar rats were taken as an animal group. The animal group were divided in four A, B, C and D groups. Four doses i.e. 2, 4, 8,16 mg of tamoxifen were injected in A, B, C and D groups respectively. For both groups i.e. human and animal group a suitable control group was selected. Visual evoked potential was tested for all subjects either human or animal group. Latency (msec) of VEP, P100 peak was measured in total cases. SPSS version 13 software program was used to analyze the data obtained.

Result: It was found out that 40% of human population in human group & C & D of animal groups had abnormal VEP which reflect it self in delay of VEP, P100 peak.

Conclusion: From the results of present work one can conclude that tamoxifen certainly has adverse effect on visual pathway which can be proved by VEP examination but in this respect dose of tamoxifen is important which will be discussed in detail in full paper.

Introduction

Breast cancer is a kind of cancer that develops from breast cells. Breast cancer usually starts off in the inner lining of milk ducts or the lobules that supply them with milk. A malignant tumor can spread to the other parts of the body [1].

The vast majority of breast cancer cases occur in females. It is the most invasive cancer in females' world wide. It accounts for 16% of all female cancers and 22.9% of invasive cancers in women. 18.2% of all cancer deaths world wide, including both males and females, are from breast cancer [1].

There are different techniques used for breast cancer treatment. Radiation therapy or in other word radiotherapy, surgery, Biological therapy, chemotherapy and hormone therapy are the main procedures for breast cancer treatment. [2]

Tamoxifen is one of hormone therapy usually prescribed for breast cancer therapy. Tamoxifen is an antagonist of estrogen receptor in breast tissue via its active metabolite, 4-hydroxytamoxifen. In other tissues such as the endometrium, it behaves an agonist, and thus may be characterized as a selective estrogen receptor modulator. Tamoxifen is the usual endocrine (anti- estrogen) therapy for hormone receptor- positive breast cancer in pre-menopausal women, and is also a standard in post-menopausal women although aromatase inhibitors are also frequently used in that setting [3].

Tamoxifen despite its advantages in breast cancer treatment has also certain side effects such as vaginal dryness, discharge or irritation, endometrial hyperplasia, endometrial cancer, deep vein thrombosis, pulmonary embolism and finally central nervous system disturbances [4].

Visual pathway is a tiny part of central nervous system that may be affected by tamoxifen medication [5].

There are different techniques for screening visual pathway disturbances. Magnetic resonance imaging (MRI) and visual evoked potential (VEP) are among the techniques which may be used in this respect. It is a well known fact that MRI is a suitable technique for structural changes in visual pathway where as VEP is a technique to indicate the functional status of visual pathway [6].

In the present research work we looked for toxic effect of tamoxifen on visual pathway using VEP technique.

Material and Method

Twenty five female patients with tamoxifen prescription for breast cancer treatment were selected. The age ranges of the patients were from 35-50 years. Visual evoked potential was tested in total patient group. Latency of VEP, P100 peak was measured in total population.

Twenty five healthy female populations with healthy visual system and same age range of patients i.e. 35-50 years were selected as a control group. Again VEP was tested in control group too. Latency of VEP, P100 peak was measured in healthy group.

Biomedical electrophysiological Mangoni instrument was used to record VEP in total patients & healthy population. Three electrodes were used to connect the subjects to the machine. Active, reference & ground electrodes were attached to occipital, earlobe & forehead respectively.

SPSS version 13 computerized software was used to analyze the results obtained in two case & control group.

Along with human population, 25 wistar rats were taken

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into consideration. They were divided in five groups i.e. A, B, C, D, E.

For animal group a solution of tamoxifen with different concentration was prepared. Normal saline and alcohol was used as a solvent. Four solution of tamoxifen with 2, 4, 8 and 16 mg concentrations were prepared for A, B, C & D groups of rats respectively. Different doses of tamoxifen solutions were calculated according to LD 50 for wistar rat. A separate solution of only alcohol and normal saline was prepared for E group, which was taken as control group. The solutions were injected intraperitoneally to each group. On sixth day VEP was tested for each animal. Again like human group, latency of VEP was measured in animal population. SPSS version 13 software was taken into consideration to analyze the result obtained in these groups as was done in human group.

Result:
The research was done in two groups. The first group (25 controls + 25 cases) was 50 human subjects. The mean latency ± S.D of VEP, P 100 peak for control group was 95 ± 5 (msec). In this group we found 10 out of 25 had abnormal VEP (i.e. 40%).

Five group of rats (A, B, C, D, E) were selected and VEP was measured in rat groups. A, B, C and D as case groups and E as a control group, The mean latency ± S.D of VEP P100 peak for control group was 100 ± 11.5 (msec). In A group we had normal VEP measurement in total rats. In B group one out of 5 rats had abnormal VEP (i.e. 20%). In C group we had four out of five abnormal VEP (i.e. 80%) and finally in last group we had all rats with abnormal VEP recording (i.e. 100%). The differences between case and control group for abnormal VEP, P100 peak latency was considered with $P<0.05$.

Discussion:
Drugs are used by human beings to treat the pathological conditions, but beside their advantages they may have different side effects that may harm the other healthy organs of the body. Tamoxifen is a drug which is used in patients suffering from breast cancer. It is observed that some of the patients using this drug complain from visual disturbances.

Moreover it was observed that these patients have normal visual examinations therefore a research was planned to check the visual pathway of these patients. The characteristics of present work are the technique used in this work i.e. visual evoked potential because there are no references in this connection. In fact for drug toxicity & pathological condition of visual system mainly the Electroretinography (ERG) & Electrooculography (EOG) are taken into consideration. [7-11]

According to result of present work 40% of patients using Tamoxifen had abnormal VEP recording. It is a proof that the visual pathway of these patients are deteriorated but we could not be certain that the malfunction is the result of Tamoxifen only because some of these patients uses the combinations of some drugs for breast cancer treatment, moreover the abnormal VEP may be due to metastasis of cancerous cells to visual pathway and finally the patients may have some of pathological problem in their medical records like multiple sclerosis that may affect the VEP recording of such patients, therefore we designed a research in wistar rats to overcome this discrepancy. In this connection a group of wistar rats were taken & Tomoxifen solution was injected in animal group to look for the toxic effect of Tamoxifen only on visual pathway.

In group A the VEPs recorded were within normal range. In group B only one rat has abnormal VEP.

In group C where the dose was twice the B group we had four out of five abnormal VEP & finally the condition was worse in D group where the dose was four time higher than B group. In addition to VEP abnormalities which was mostly reflected in latency of VEP, P100 peak in D group we observed sight problem, muscle weakness & balance abnormalities which were clear from change in rats' activities. These findings indicate that low doses of tomoxifen have no toxic effect on visual pathway where as high doses of tomoxifen certainly affect the visual pathway which can be diagnosed by abnormal VEP.

Gorin et al worked on the effect of tamoxifen on visual system of patients suffering from breast cancer following tamoxifen treatment. They found that the women treated by tamoxifen had no difference in the activities of daily vision, visual acuity measurements or other test of visual function [12]. In fact such type of result i.e. normal Vision with low dosage of tamoxifen is reported by other research worker in related field [13-14]. These references support the results of present work particularly when human subject with standard dose of drug is used for breast cancer treatment.

Cho et al administered tamoxifen to adult mice at different ages by intraperitoneal injection. The effect was rapid retinal ganglion cell (RGC) loss, reactive gliosis, progressive degradation of optic nerve over period of several months and visual impairment [15].

Same result is reported by other research workers in this connection [16-17]. These changes in retina can increase latency of VEP, P100 peak [5, 13, and 18]. Again these references support the results of present work mostly when animal sample with high dosage of tamoxifen is used.

Conclusion
Tamoxifen is a drug for breast cancer treatment**.** Low doses of tamoxifen does not affect visual pathway where as high dosage of it harms the visual pathway which can be diagnosed by visual evoked potential.

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