EFFECTS OF TAMOXIFEN ON LIPID PROFILE, SERUM CALCIUM AND GONADOTROPIN LEVELS IN CARCINOMA BREAST PATIENTS

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ABSTRACT

BACKGROUND

Breast cancer is the second most common cancer in females in India. The regional cancer centre Thiruvananthapuram statistics show a steady increase in breast cancer every year. The anti-oestrogen Tamoxifen is used in long-term treatment of carcinoma breast and is also used as a chemo-preventive agent to subjects who are at high risk for carcinoma breast. Tamoxifen belongs to triphenyl ethylene group of oestrogen compounds. Pharmacological actions are both oestrogenic and anti-oestrogenic. In postmenopausal women, it is known to have oestrogen-like effects on bone density and on lipid metabolism. Anti-oestrogenic effects of tamoxifen may be exerted at hypothalamic or pituitary level. Drug opposes the negative feedback effect of oestrogen and blocks the inhibitory action of oestrogen on LH release.

MATERIALS AND METHODS

The study was a case control study. Hundred patients from Thiruvananthapuram Regional Cancer Centre, who were on treatment with tamoxifen for 1 to 4 years were taken as test group and fifty persons with carcinoma breast who were not taking Tamoxifen were taken as the control group. A proforma was given to assess the adverse effects of the drug like h/o profuse vaginal bleeding, nausea and vomiting or joint pains. The proforma also contained the risk factors of carcinoma breast like age at menarche, age of first child birth, premenopausal/postmenopausal and family h/o breast cancer.

Inclusion Criteria- 1. Carcinoma breast patients who were not on radiotherapy or chemotherapy at the time of study; 2. Patients who came for review in Regional Cancer Centre Radiotherapy Unit I, Trivandrum, who were on Tamoxifen.

Exclusion Criteria- 1. Carcinoma breast patients who were on radiotherapy or chemotherapy at the time of study; 2. Patients who were having terminal disease on palliative treatment; 3. Patients who were not willing for the study.

Parameters Taken- 1. Lipid Profile, A. HDL cholesterol, B. LDL cholesterol, C. Triglycerides; 2. Serum Calcium; 3. Total Proteins; 4. Luteinising Hormone.

As calcium is bound to total protein, it was also included. The study and control groups were further divided into premenopausal and postmenopausal groups. Post-menopausal group was mostly oestrogen receptor positive. Medical software was used for statistical analysis.

RESULTS

Comparison of total cholesterol and LDL cholesterol in test group and control group as a whole showed a reduction in test group, which was significant statistically. No statistically significant results were obtained on comparing serum calcium serum protein and LH in test and control group as a whole. Comparison of lipid profile in postmenopausal test group when compared to postmenopausal control group showed a reduction in total cholesterol, which was significant statistically. LDL cholesterol was reduced in the test group, which was statistically significant. Other parameters did not show statistically significant results.

CONCLUSION

From the questionnaire given in the proforma, it was concluded that Tamoxifen did not have any specific toxic adverse effect. It was more effective in postmenopausal patients, as they were oestrogen receptor positive. It had oestrogen like effects on lipid profile, which was favourable. There was no unfavourable effect on hypothalamo-pituitary axis, as it caused no variation in LH. So Tamoxifen can be used as a safe drug for long-term treatment of breast cancer preventing metastasis and contralateral breast cancer. It can also be used for chemoprophylaxis in healthy women who were at high risk for carcinoma breast.

KEYWORDS

Carcinoma Breast, Tamoxifen, Lipid Profile, Serum Calcium, Gonadotropins.

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BACKGROUND

Breast cancer is the most common cancer in females in India. National cancer registry programme 2012 - 2014 shows increased incidence of breast cancer among younger age group, increase in incidence of carcinoma in India and also late presentation and lack of awareness on screening directly reduces the long-term survival of the victims. Early menarche, late menopause and nulliparity increase the risk of breast cancer. BRCA1 and BRCA2 genes are responsible for the lifetime risk of breast cancer.[1] Epithelial transforming growth factor, Alpha and Beta insulin-like growth factors 1 and 2 influence the growth of breast cancer cells. Cytokines and lymphokines also influence the phenotypic effect of breast cancer.[2]

Anti-oestrogen Tamoxifen chemically belongs to the triphenyl ethylene class of compounds. It was given for

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patients with node negative, oestrogen receptor positive post-menopausal women and also for node positive and all cases of metastasis. Tamoxifen is a long acting anti-oestrogen with both oestrogenic and anti-oestrogenic effects. They block estradiol from binding to the receptors.[3] The aim of the study is to find out the adverse effects of long-term use of Tamoxifen on patients with carcinoma breast.

Review of Literature

Anti-oestrogen Tamoxifen is the hormonal agent used for treatment of carcinoma breast. It was first identified by Harper and Walpole in 1956. Tamoxifen belong to the triphenyl ethylene group of compounds with both oestrogenic and anti-oestrogenic actions.[4] Tamoxifen has oestrogen like effects to enhance bone density in prevention of osteoporosis.[5] It has oestrogen like beneficial effect on lipid metabolism.[3] The drug inhibited negative feedback effects of oestrogen at the hypothalamo-pituitary level on LH release. The mechanism of action of Tamoxifen is that it blocks estradiol binding to its receptors.[6] It binds to oestrogen receptor and cause nuclear accumulation of antagonist receptor complex. This accumulation is accompanied by long-term depletion of cytosolic receptor complexes. All these effects cause altered receptor function. The discovery of oestrogen receptor led to speculation of hormonal dependence of tumour. Oestrogen is lipid soluble and the molecules diffuse through the cell membrane into the interior of the cell. Oestrogen receptor located in the cytoplasm after binding to oestrogen receptor undergo transformation step prior to translocation. Unbound oestrogen receptor resides in the nucleus.[7] Hormone receptor complex bind to nuclear chromatin and alters the transcription of specific mRNA and codes for translation of specific proteins. Two growth factors IGF1 and TGF have been reported to be secreted products found in cultured human breast cancer cells.

There is found to be good co-relation between oestrogen receptor and menopausal status. Postmenopausal patients are mostly ER positive and respond to hormonal therapy; 90 percent of ER negative patients do not respond to hormonal therapy due to heterogeneity of the tumour. Antitumour effect of Tamoxifen is by inactivating calcium conductance in tumour cells. It induces deregulation of calcium in human breast cancer cells by acting as an oestrogen antagonist.

Tamoxifen is absorbed following oral administration with peak level after 4 to 7 hours and steady level after 4 to 6 weeks. The drug is converted to 4-hydroxy N methyl Tamoxifen, which retains high affinity for ER.

Adverse Effects

Hot flushes, nausea, vomiting, vaginal bleeding, joint pains and osteoporosis[4] compared to healthy control visual memory, word fluency and immediate verbal memory loss was reported in a recent study.[8]

Effects of Tamoxifen on Lipid Profile, Serum Calcium and Gonadotropins

It alters lipid profile favourably. It has oestrogen like effect on bone metabolism preventing osteoporosis.[3] Estimation of serum protein is essential as calcium is bound to plasma protein. It has anti-oestrogenic effect on gonadotropins. It opposes the effect of oestrogen by increasing pituitary FSH and LH.

MATERIALS AND METHODS

Study done was a case control study. Study group and control groups were selected from carcinoma breast patients who were attending the outpatient clinic of Regional Cancer Centre, Thiruvananthapuram. The study group patients and test group had either radiotherapy or chemotherapy or both earlier and were under scrutiny. Then study group patients were on Tamoxifen for 1 to 4 years and test group patients were not on Tamoxifen therapy.

Sample size was calculated according to the equation

$n= (2 \times (1-\alpha/2)^2 \times P (1-P))/D^2$

p- Prevalence.

D- Confidence interval.

With a prevalence of 75% sample size was calculated taking,

P= 75, D= 25% of 75 i.e. 80

$\alpha/2$= 3.84 (corrected to 4)

Hence, $n= (2 \times 9 \times 75 \times 25)/(18 \times 18) = 104$

Therefore, rounding the figure sample size of test group was taken as 100 and sample size of control was taken in the ratio 1:0.5 the sample size of test and control group was 100 and 50 respectively.[9]

A proforma was given to the patients with questionnaire on any of the risk factors for carcinoma breast like age at menarche, age at first child birth, h/o lactation, use of oral contraceptives, hereditary or family h/o carcinoma breast and whether they had any other malignancies. The proforma also contained the details of adverse effects of drugs like profuse vaginal bleeding, hot flushes, nausea/vomiting, h/o thromboembolic events or h/o joint pains.

The test group and control group were further divided into premenopausal and post-menopausal groups. The patients were seen in the outpatient clinic of Radiotherapy Unit 1 in Regional Cancer Centre, Trivandrum; 9 mL blood were collected from fasting patients. Details of proforma were collected and analysed. Medical software was used for statistical analysis.

List of Biochemical Parameters

1. Lipid profile.
    a. Total cholesterol.
    b. LDL cholesterol.
    c. HDL cholesterol.
    d. Triglycerides.
2. Serum calcium.
3. Total protein.
4. Albumin.
5. Luteinising hormone assay.

RESULTS

All the test groups and control groups were analysed.

1. Whole test groups were analysed against control groups.
2. Premenopausal test group was analysed against premenopausal control groups.
3. Post-menopausal test groups was analysed against post-menopausal control groups.

Analysis of risk factors of carcinoma breast in study and control groups were analysed separately. Adverse effects following Tamoxifen therapy were also analysed from the questionnaire in the proforma.

Analysis of Risk Factors of Carcinoma Breast in Study and Control Group

It showed that mean age of occurrence of carcinoma breast was 48 years. Family h/o joint pains was found in only 7% of cases. Mean age of first child birth was 24 years and mean age at menarche was 13 years. Adverse effects following Tamoxifen therapy observed were not of statistical significance. Only 7% had h/o joint pains. Excessive bleeding and nausea/vomiting were found in only 1% of study group and thus were not statistically significant.

The Comparison of Lipid Profile in Whole Test Group and Control Group (Table 1 and Chart 1)

It showed a reduction in total cholesterol and LDL cholesterol in test group compared to control group, which was statistically significant. Plasma triglyceride and HDL cholesterol level showed no difference, which was of significance statistically. Comparison of serum calcium, serum protein and luteinising hormone in test and control group showed no significance statistically.

Comparison of Premenopausal Test Group with Premenopausal Control Group

It showed no difference in levels statistically of total cholesterol, LDL, HDL and triglycerides. Comparison of serum calcium, proteins and luteinising hormones also showed no statistical difference between premenopausal test and control group.

Comparison of Lipid Profile in Post-Menopausal Test with Post-Menopausal Control Group (Table 2 and Chart 2)

Total cholesterol in postmenopausal test group showed a reduction compared to the control group, which was statistically significant. LDL cholesterol also showed a reduction in the postmenopausal test group compared to the control group, which was of statistical significance. Triglycerides also showed a reduction of statistical significance in the test group.

No change of statistical significance was observed between post-menopausal test and control group with respect to serum protein, calcium and LH (Table 3 and Chart 3).

Student 't' test and chi square test were used for statistical analysis.

Haematological Finding Test	Test Group	Control Group	T Value	P Value
	x̄ ± SD	x̄ ± SD		
Total Cholesterol	204.6 ± 47.2	225.2 ± 37.0	1.72	P < .05
LDL mg/dL Cholesterol	121.9 ± 48.4	148.3 ± 41.9	2.063	P < .05
HDL mg/dL Cholesterol	51.0 ± 21.6	47.0 ± 21.4	0.66	P >.05
Triglycerides mg/dL	176.3 + 91.6	140.4 + 61.3	1.62	P >.05

Table 1. Comparison of Lipid Profile in Test Group and Control Group as a Whole

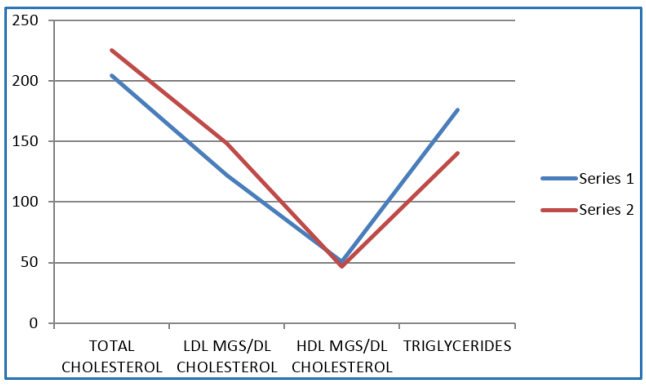

Chart 1. Comparison of Lipid Profile in Test Group and Control Group as a Whole

Haematological Findings	Post-Menopausal Test Group	Post-Menopausal Control Group	T Value	P Value
	x̄ ± SD	x̄ ± SD		
Total Cholesterol mg/dL	205 ± 49.9	228.5 ± 34	2.46	P < .05
LDL Cholesterol mg/dL	121.3 ± 51.3	154.8 ± 31.5	3.52	P < .01
HDL Cholesterol mg/dL	52.2 ± 23.2	49.5 ± 35.6	0.40	P > .05
Triglycerides mg/dL	179.6 ± 96.4	119.1 ± 31.5	11.6	P < .001

Table 2. Comparison of Lipid Profile in Post-Menopausal Test with Post-Menopausal Control Group

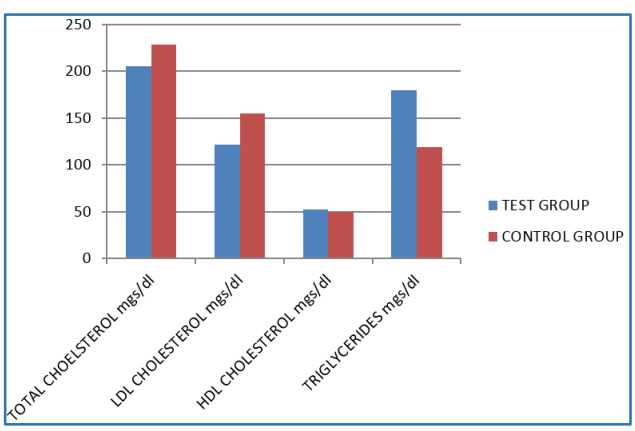

Chart 2. Lipid Profile in Post-Menopausal Test and Control Group

Haematological Findings	Post-Menopausal Test Group	Post-Menopausal Control Group	T Value	P Value
	x̄ ± SD	x̄ ± SD		
Serum Calcium mg/dL	8.42 ± 1.12	8.24 ± 0.77	0.84	p >.05
Total Protein mg/dL	6.24 ± 1.12	6.43 ± 0.46	1.0	p >.05
Albumin mg/dL	4.29 ± 0.9	4.65 ± 1.2	1.33	p >.05
LH IU/L	21.12 ± 10.2	25.56 ± 19.24	1.1	p >.05

Table 3. Comparison of Serum Protein Calcium and LH in Post-Menopausal Test and Control Group

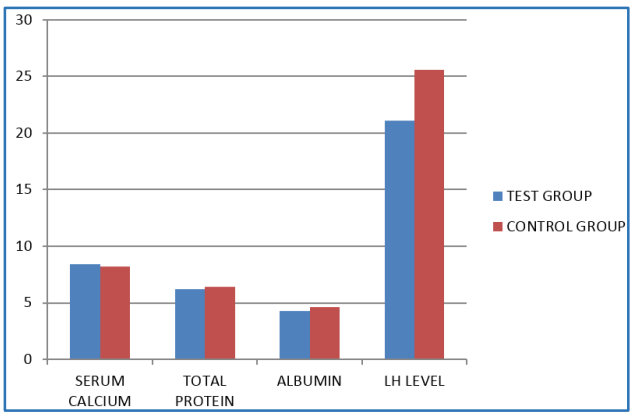

Chart 3. Serum Protein, Calcium and LH in Post-Menopausal Test and Control Group

DISCUSSION

In our state of Kerala, carcinoma breast is the leading cancer among women. In the present study, an attempt was made to identify whether any particular risk factor was seen in our epidemiological setting. Analysis of risk factor in study and control group did not give any risk factor, which was of statistical significance in the questionnaire given. The adverse effects of Tamoxifen observed also did not give values of statistical significance. Only 7% had joint pains in the study group and excessive bleeding and loss of appetite and nausea were found in only 1% of cases.

Lipid Profile

(Table 1 and Chart 1) shows the comparison of lipid profile between test group and control group as whole. The total cholesterol and LDL cholesterol were reduced in the test group, which was significant statistically. Comparison of lipid profile between premenopausal test group and control group showed no difference of statistical significance as premenopausal patients were oestrogen receptor negative. Tamoxifen was more effective in oestrogen receptor positive post-menopausal patients. (Table 2 and Chart 2) shows comparison of lipid profile between post-menopausal test and control group. The inference shows that there is favourable alteration in lipid profile in oestrogen receptor positive post-menopausal patients. Total cholesterol and LDL cholesterol were reduced in the test group. These 2 factors are important risk factor in the prevention of atherosclerosis. In normotensive rats,[9] LDL cholesterol ingresses into subendothelial space causing further oxidative damage and imbalance the ability of macrophages to scavenge the lipoproteins are saturated. Studies by Constantino J P showed a reduction in incidence of ischaemic heart disease in patients on Tamoxifen. Journal of cardiovascular pathology explains that fall in LDL levels are achieved by upregulating apo B100/E receptors in liver and other sites.[6] LDL particles are rapidly taken up from plasma compartments, thereby altering their plasma level and also reduce the clearance and synthesis of LDL and thus reducing the LDL. The increase in HDL is achieved by increasing hepatic synthesis of key HDL apoprotein A, resulting in over production of HDL. The increase in triglyceride noted in post-menopausal age group may be due to the anti-oestrogenic effect of Tamoxifen.[10]

It can be concluded that Tamoxifen exert oestrogen like beneficial effect on lipoprotein lowering total cholesterol and LDL levels significantly. Though HDL levels could not be proved statistically, study gives a favourable HDL/LDL ratio which is normally less than 5.

Serum Calcium

Comparison of serum calcium in whole test and control group showed no difference of statistical significance. Tamoxifen inhibit calcium calmodulin or calcium phospholipid activated protein kinase. This is one of the methods suggested for tumour suppressor effect of Tamoxifen. Study in ovariectomised mice showed oestrogen like effect in preventing bone loss and weight of uterus. One study showed the drug was recently shown to inhibit growth of cultured foetal rat metatarsal bone and was thought to effect bone growth in vivo.[11] Tamoxifen act as an oestrogenic agonist in bone metabolism in primary hyperparathyroidism.[12] Total protein and albumin were included in study as calcium is bound to protein. Any interpretation for given value for total plasma calcium is impossible without correction for concentration of plasma protein (Table 3 and Chart 3).

Effect on Luteinising Hormone

A comparison of luteinising hormone between whole test and control group and comparison of post-menopausal test and control group showed no difference of statistical significance. (Table 3 and Chart 3) Oestrogen is known to exert a negative feedback effect on LH secretion. Tamoxifen opposes the negative feedback effect of oestrogen on LH release due to its anti-oestrogenic effect. Table 3 showed only a numerical reduction in LH. Study showed that at the time of menopause there is a three-fold increase in LH reaching a maximum at 1 to 3 years after menopause causing the disappearance of ovarian follicles. The elevated gonadotropins dried the remaining stromal tissue in the ovary to a level of increased testosterone secretion.[13]

Studies showed many diverse effects on sex hormone[14] levels, but does not influence the biological status of the individual.

CONCLUSION

The study was selected because carcinoma breast is a leading cancer in the State of Kerala and the incidence is increasing each year. No risk factor for carcinoma breast was predominantly seen in our epidemiological setting. Long term use of Tamoxifen did not have any specific toxic effects.

The most striking observation was the favourable alteration it produced in lipid profile. There was reduction in total cholesterol and LDL cholesterol, which was more marked in post-menopausal women.

The drug Tamoxifen did not produce any change in serum calcium, so it did not have any unfavourable effect on bone. Tamoxifen had no effect on luteinising hormone, which showed it produced no unfavourable alteration in hypothalamo-pituitary axis.

From the present study, it can be concluded that Tamoxifen is a safe drug which can be used for long-term treatment of breast cancer preventing metastasis and contralateral breast cancer. Tamoxifen can be used for chemoprophylaxis in healthy women who are at high risk for developing carcinoma breast without fear of adverse effects.[15]

Information this study offers: The drug tamoxifen without fear of its side effects can be administered for carcinoma

breast patients to prevent recurrence, contralateral breast cancer and metastasis. It can also be given to healthy adult females, who are at high risk for carcinoma breast.

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