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Original Article

Gynecological abnormalities in relation to tamoxifen therapy

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Abstract

Objectives : To study the effects of tamoxifen use on endometrium, myometrium, and adnexae in patients with breast carcinoma on tamoxifen therapy. *Methods :* Study group (n=25) included patients of breast carcinoma on tamoxifen therapy, control group (n=50) included age matched breast carcinoma patients not on tamoxifen therapy and women with no gynecological problems. Transvaginal sonography (TVS) was performed in them. Symptomatic patients or with abnormal TVS findings had endometrial aspiration biopsy. *Results :* 44% in study group had abnormal TVS findings as compared to 2% in control group (p value<0.001). The mean endometrial thickness was higher in study group (p value =0.001). 60% in study group with abnormal histopathology were asymptomatic. Incidence of thickened endometrium in patients on tamoxifen for <5 years was 31.57% as compared to 16.67% for >5 years. *Conclusion :* Study confirms potential side effects of tamoxifen in asymptomatic breast carcinoma patients, especially postmenopausal. There is a definite need for routine monitoring and availability of a safer adjuvant agent with similar efficacy.

Key words : tamoxifen, breast carcinoma, endometrium, transvaginal sonography

Introduction

Tamoxifen has revolutionized the management of breast cancer patients since its introduction in 1969. Due to its partial agonist activity on estrogen receptors, tamoxifen seems to increase the risk for endometrial lesions. Some reports[1] have cited an increased incidence of abnormalities such as hyperplasia, polyposis, carcinoma and sarcoma in women on tamoxifen therapy. Due to this many recommendations have been made regarding routine screening of these women for endometrial cancer[2]. The present study was undertaken to evaluate the effects of tamoxifen use on endometrium, myometrium, and adnexa when used in patients with breast carcinoma. The relative effect of duration of tamoxifen therapy was also studied in the Indian population.

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Methods

A case control study was carried out in the Department of Obstetrics and Gynecology, King George's Medical University (KGMU) Lucknow, India from May 2002 to July 2003. A total of 75 subjects were studied which included 25 subjects in study group (A) and 50 subjects in control group (B). In group A, 4 were premenopausal and 21 were postmenopausal while in group B, 10 were premenopausal and 40 were postmenopausal. Inclusion criterion for group A was biopsy or cytology proven

breast carcinoma patient treated by surgery with or without radio-chemotherapy and then put on tamoxifen as an adjuvant therapy in dose of 10mg twice daily or 20mg once daily for more than 6 months. Inclusion criteria for controls were age matched women with no gynecological problems and breast carcinoma patient not on tamoxifen therapy. The exclusion criterion for both groups was the use of any form of hormone replacement therapy in last six months. All subjects were evaluated by taking detailed history followed by general, systemic and gynecological examination. All of them underwent pap smear examination and TVS. The uterus was scanned both in sagittal and coronal section to determine the regularity and thickness of endometrium. In postmenopausal patients, endometrial thickness <5mm was considered normal while in premenopausal patients, the normal value varied with menstrual phase (during menstruationg thin broken echogenic line, proliferative phaseg hypoechoic, 4-8mm, secretory phaseg hyperechoic, 7-15 mm)[3]. Any deviation from the above was labeled as abnormal endometrium. Abnormalities in the myometrium or adnexa were also noted. Patient with history of abnormal vaginal bleeding, abnormal Pap smear, and endometrial thickness more than expected for the menstrual phase or any other abnormality on TVS were subjected to endometrial aspiration biopsy for histopathological examination. The statistical analysis of the data so obtained was performed using SPSS 10.0 for Windows 98/Xp.

Results

The two groups were compared for the baseline characteristics like age, parity, age at menarche, age at first delivery, age at menopause, body mass index (BMI), diabetes, hypertension, and treatment given for breast carcinoma. There was no statistically significant difference in the two groups except for mean BMI, which was higher in the study group (p=0.003).

Table 1 shows the comparison of TVS findings in the two groups which are suggestive of statistically significant risk of endometrial and myometrial anomalies in study group (p<0.001). In group A, the endometrial thickness ranged from 1-15 mm with mean endometrial thickness of 4.84mm (SD±3.35) and 28% patients had thickened endometrium. In group B, endometrial thickness varied between 2-14mm with mean endometrial thickness of 4.02mm (SD±2.61) but only 2% had thickened endometrium. The mean endometrial thickness in patients with abnormal TVS finding was 6.5mm, while in patients with normal TVS findings the mean endometrial thickness was 3.3mm, the difference being statistically significant (p value 0.013).

50% of premenopausal patients of study group had abnormal TVS findings (fibroid, ovarian cyst, thickened endometrium) while none of the premenopausal patients in control group had any abnormality on TVS (p value <0.001).

36% (9/21) of postmenopausal patients in group A had abnormal TVS finding (thickened endometrium, fibroid, adenomyosis, endometrial polyp, ovarian cyst) while only 2% (1/40) of the postmenopausal patients of group B had abnormal findings on TVS (thickened endometrium & fibroid). The difference is significant (p value <0.001).

Mean endometrial thickness in the two subgroups of the control group did not show statistically significant difference. Out of 11 patients of group A with abnormal TVS findings, 5(45.46%) were symptomatic and 6(54.54%) were asymptomatic while only one patient of group B had fibroid and was asymptomatic.

Table 1. Transvaginal sonographic findings in the study group and the control group.

Abnormal TVS findings	Study group (n=25)	Control group (n=50)	P value
Fibroid	4	1	
Polyp	1	0	
Adenomyosis	7	0	
Ovarian cyst	3	0	
Thickened endometrium	7	1	
Abnormal TVS findings n (%)	11(44%)	1(2%)	<0.001[a]

'[a]' - by fisher's exact test

Table 2. Comparison of histopathological findings in the study group and the control group.

Histopathological findings	Study group (n=11)	Control group (n=1)
Normal endometrium	5 (44.45%)	0
Atrophic endometrium	1 (9.1%)	0
Proliferative endometrium	0	0
Endometrial polyp	1 (9.1%)	0
Simple hyperplasia	4 (36.36%)	1
Complex hyperplasia	0	0
Atypical hyperplasia	0	0
Endometrial carcinoma	0	0

Table 3. Comparison of positive predicative value of transvaginal ultrasound in different studies.

Study	No. of patients who underwent biopsy	Cut off limit of abnormal endometrial thickness (mm)	Symptomatic/ Asymptomatic/ Mixed	Abnormal histopathologic findings (%)
Cohen et al (1993)[12]	71	5	Asymptomatic	8
Cecchini et al (1996)[13]	108	6	Asymptomatic	1.85
Kedar et al (1994) [14]	Not available	8	Asymptomatic	100
Cheng et al (1997) [5]	33	6	Symptomatic	67
Present study	8	5	Mixed	83.33[a] 80[b]

'a' - including both premenopausal and postmenopausal patients
'b' - including only postmenopausal patients

Table 4. Comparison of different cut off limits of endometrial thickness in relation to sensitivity and PPV in our study.

Cut off limit	Sensitivity (%)	PPV (%)
5 mm	100	80
8 mm	80	100

According to the criteria described previously, 14 patients were eligible for endometrial biopsy but 2 dropped out. As shown in Table 2, 50% of the patients had abnormal histopathology but none of them had malignant lesion.

In group A, the duration of tamoxifen therapy ranged from 6 to 84 months with a mean of 36 months. The mean duration of tamoxifen treatment in patients with abnormal TVS finding was 41.3 months while in patients with normal TVS findings was 31.08 months. The difference was not significant (p value 0.25).

Discussion

Tamoxifen is an important drug used for adjuvant therapy in the management of breast carcinoma patients. However, after the publication of article[4] in 1988 it was clear that further evaluation is mandatory before the 'undisputed' safety of tamoxifen could be accepted.

The screening protocol used in the present study was similar to the screening protocol proposed by Burgmann et al[2]. In the present study, the demographic characteristics of the study group and the control group were similar except for BMI, thus nullifying the effects of risk factors on the endometrium, myometrium, and adnexa. Significantly higher BMI found in the study group is consistent with the fact that the obesity may be a risk factor for breast carcinoma. Most of the patient with thickened endometrium in the study group had higher BMI.

Effects of tamoxifen on endometrium, myometrium and adnexae

In the present study, 44% of patients in group A had abnormal TVS findings, of which 8% were premenopausal and 36% were postmenopausal indicating greater effect of tamoxifen on postmenopausal patients.

Overall 7(28%) patients in the study group and 1(2%) in the control group had thickened endometrium (P=0.001). Our results in postmenopausal patients showed an increased mean ET in group A as compared to group B patients (p value 0.091). Similar endometrial changes have been reported in the studies conducted by Cheng et al[5]. In our study, the proportion of patients with thickened endometrium in the premenopausal study group was also higher in comparison to the premenopausal control group. This is unlike the results of the study by Cheng et al[5] wherein the phase of menstrual cycle when patients were evaluated has not been specified.

The mean endometrial thickness in the two subgroups of the control group has not shown any statistical difference emphasizing that primary treatment of breast carcinoma does not have any significant effect on endometrium.

Occurrence of endometrial cancer in patients with breast carcinoma on tamoxifen therapy has already been reported in several studies[1,4,5]. As shown in Table 2, the only abnormal histopathology found in our study group was simple hyperplasia (n=4; 36.36%) which has 1% chance of progression to endometrial carcinoma[6].

Duration of tamoxifen and its effect

In our study it was found that 27.77% of the patients developed endometrial lesions after two years of tamoxifen therapy while 28.57% developed lesions within two years. The difference was found to be insignificant. This was unlike the reports by the other authors[7-9]. The incidence of thickened endometrium in patients on tamoxifen for <5 years was 31.57% as compared to 16.67% in patients on tamoxifen for >5 years, emphasizing the need for strict follow-up in the initial 5 years of tamoxifen therapy.

Effects of tamoxifen and clinical symptoms

According to the report of NSABP trial[10], the risk of developing endometrial cancer are outweighed by the significant benefit provided by tamoxifen therapy, therefore close scrutiny of the tamoxifen treated cohort is required. In our study also it was found that 45.46% patients with abnormal TVS findings were symptomatic. Only 2(40%) patients with abnormal histopathologic findings were symptomatic. Thus, all patients irrespective of their clinical symptoms should be screened for endometrial pathology.

Diagnostic accuracy of TVS for endometrial abnormalities

Because of high sensitivity (100%) and optimum PPV (80%) of TVS it can be used as a good screening procedure. This is similar with the findings of Tesoro et al[11] who reported a sensitivity of 84% of transvaginal sonography to detect endometrial abnormality. Cohen et al[12] found that TVS had a sensitivity of 91% and specificity of 96% for detection of endometrial diseases.

The positive predictive value (PPV) of TVS for detecting abnormal histopathology is 83.33% Table 3 shows the marked variation of PPV reported in literature. It could be due to different cut off limits of endometrial thickness. In our study, increasing the cut off limit of thickened endometrium to 8mm led to missing of 16.67% of cases and a decrease in the sensitivity of TVS as a screening tool. Thus cut off value of thickened endometrium should be taken as 5mm (Table 4).

Tamoxifen treatment is reported to induce endometrial

stromal hyperplasia[15] which can lead to high false positive rate on transvaginal sonography if used for screening these patients. Goldstein[15] suggested the use of sonosalpingography to overcome these shortcomings. The present study confirms the potential side effects of tamoxifen on uterus and adnexa. It serves to emphasize the importance of monitoring in breast carcinoma patients who are taking this drug as an adjuvant therapy especially in first two years of therapy. A routine periodic gynecological follow-up with TVS followed by endometrial aspiration in symptomatic patients and patients with endometrial thickness more than 5mm is recommended.

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