Tamoxifen gynecological side effects

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الخلاصة :
دراسة استباقية اجريت في مستشفى الولادة و الطفل بلتعاون مع قسم الامراض السرطانية فيمستشفى الصدر التعليمي لمدة سنتين 2002-2004 لتبين مدى تاثير العقار على ارحام النساءالمصابات بسرطان الثدي باعتبار ان التوموكسوفين يزيد من احتمالية الاصابة بسرطان الرحم او التغيرات التي تسبق الاصابة بسرطان الرحم
الهدف
مقارنة تاثيرات الجانبية العقار التوموكسوفين على النساء المصابات بسرطان الثدي قبل و بعد سن الياس
طرق الدراسةو النتائج
تم تقسيم المرضى الى مجموعتين ما قبل سن الياس و المجموعة الثانية ما بعد سن الياس تشكو من اعراض حيث تم اخذ التاريخ المرضي ثم فحص المجموعتين وبعدها تم فحص المجموعتين بجهاز السونار (الموجات فوق الصوتية) لتبين التغيرات في الرحم ثم اجراء مسحة من الرحم تحت التخدير العام و كانت النتائج كما يلي
اغلب المرضى 45,8%تقع بين الفئة العمرية 50-60 سنة
68,7% من النساء تعاني من نزف رحمي والدي يعتبر اهم عارض
22,9% حجم بطانة الرحم اقل من 6ملم عند الفحص بجهاز السونار بينما 41,6% حجم بطانةالرحم هو اكثر من 1 سم و لم يثبت احصائيا اي اختلاف بين الفئتين تحت الدراسة
بعد اخذ المسحة تحت التخدير العام 21,2% من النساء تبين انها تعاني من ضمور البطانة الرحميةبينما 16,9% تشكو تضخم بطانة الرحم في كلا المجموعتين وانه لا يوجد الختلاف بين المجموعتين احصائيا .
المناقشة
تبين من الدراسة انه لا يوجد اي زيادة في معدل الاصابة بسرطان الرحم كتاثير جانبي لعقار التوموكسوفين في كلا المجموعتين تحت الدراسة و كما انه لا يوجد اختلاف في معدل الاصابة بتضخم الرحم الحميد او المسرطن في كلا المجموعتين
كما تبين ان جهاز السونار غير قادر على التفريق او تشخيص المبكربين التغيرات المسرطنة او الغير مسرطنة عند كلا الفئتين العمرية اي قابليته التشخيصية محدودة و احصائيا لا يوجد فرق بين المجموعتين
يعتبر النزف الرحمي اهم الاعراض و اكثرها شيوعا التي يشكومنها كلا الفئتين تحت البحث

Abstract
Prospective comparative study done in basrah maternity and child hospital over a period of two years from 2002- 2004 , on breast cancer patients treated with tamoxifen which is estrogen receptors modulators with paradoxical effects (agonist on some tissue and antagonist on others. This study aimed To compare side effect of tamoxifen on both studied groups Premenopausal and postmenopausal .
This study included96 Symptomatic pre and postmenopausal breast cancer treated patients with tamoxifen assassed by history and then examination was performed
Then endometrium assessed by transabdominal ultrasound to check thickness then almost all patients subjected to endometrial biopsy under general anesthesia, about 45.8% of patients between 50-60 years of age 41.6% of patients had advanced stages of cancer , vaginal bleeding which is the most common symptom symptoms presented in 68.7% ,while 22.8% , 8.28% had vaginal discharge and pain respectively.
ultrasound findings showed 22.9% endometrial thickness less than 6mm , 41.6% endometrial thickness 1 cm and more ,10.3% showed polyps and fibroid . no

statistical difference between pre and postmenopausal inUSS findings with p value = 7.81, x^2= 13.7, df=3
21.2% showed atrophic endometrium, 16.9% showed endometrial hyperplasia , bulk 44.6% showed non secretory (proliferative) , with no cases of endometrial carcinoma . No, statistical difference between pre and postmenopausal findingsP value = 9.49 , x^2 8.652 , df= 4 .In conclusion the main sharing symptoms in both groups was vaginal bleeding, USS had a poor predictive value in detecting changes in both studied group
Our study did not confirm risk of endometrial carcinoma , with no statistical difference in risk of hyperplasia between pre and postmenopausal studied groups

Introduction

Breast cancer is one of the mostcommon female malignancies ,due to development of mammography and others screening techniques along with adjuvant therapy more women can survive their breast cancer.([1])

Tamoxifen is selective estrogen receptors modulators and one of the most commonly used antineoplastic , approved by U.S.food and drug administration for treatment of advanced breast cancer among postmenopausal women in 1978 ([2]).

Tamoxifen reduce risk of invasive and non invasive breast cancer by 49%, 50% respectively.([3])

Its uses associated with spectrum of uterine abnormalities due to its paradoxical effect (estrogenic on some tissues and anti estrogenic on others)including benign alteration such as polyps , endometrial hyperplasia , endometrial cystic atrophy or fibroid as wellas malignant transformation into carcinoma or sarcoma . ([4])

Its effect on genital tract depend on the ambient estradiol concentration and menopausal state ([5])

In postmenopausal women the agonist is more predominant , additionally some of its metabolites such as met E has agonist effect but its role is debatable .([6])

AIM

To compare effect of tamoxifen on uteruses of premenopausal and postmenopausal women in our society .

Material and methods

Prospective study done in Basra maternity and child hospital and oncology department in Taalimi hospital in Basra over a period of two years from January 2002- 2004.

96 patients initiating tamoxifen therapy only (no other treatment modalities) at a dose of 20mg /day for 2 years from the time of surgery

For breast cancer , who had had no cancers other than breast

The symptomatic studied patients comprises two groups, premenopausal and postmenopausal breast cancer treated patients

All symptomatic patients were subjected to detailed history including(age, , menopausal state, stage of breast cancer , gynecological symptoms at presentation which were abnormal vaginal bleeding, vaginal discharge and pain).

Then followed by gynecological examination.endometrial thickness and any uterine abnormalities were studied by trans abdominal ultrasound by the same observer ,transabdominal USS was used due to patients preference

Then patients subjected to endometrial biopsy under general anesthesia and pieces of endometrium were sent for histopathological examination with same pathologist

Out of 96 patients ,94 patients did endometrial biopsy (2patients did not have endometrial biopsy because one patient was very old with sever cervical stenosis (obliterated cervix partially) so endometrial biopsy was not possible , other patient was virgin and refuse endometrial biopsy

Result

Table 1

Showed patient characteristics

44(45.8%) patients occurred between 51-60 years of age , while only 8(8.3%) patients above 61 years of age

40(41.6%) patients had early stages of breast cancer, 56(58.3%) had advanced cancer

44 (45.8%) premenopausal and 52(54.1) postmenopausal patients were participated in this study

Table 2

Showed patients symptoms

Abnormal vaginal bleeding were the most common presenting symptoms 66(68.7%) , Out of them 24(25%) premenopausal patients presented with menorrhagia

while 22(22.8%) of total patients presented with vaginal discharge : 14 (14.5%) in premenopausal and 8(8.3%) among postmenopausal patients 8(8.28%) patients presented with abdominal pain

statistically no, significant difference between two studied groups

Table 3

Showed ultrasound findings

Showed 22(22.9%)patients had ultrasound endometrial thickness ≤ 6mm while 40(41.6%) patients had endometrial thickness ≥ 1 cm , 13(13.5%) premenopausal and 27(28.1%) postmenopausal

fibroid and polyp were found in 10(10.4%) of total patients.

Statistically no significant difference in ultrasound finding between premenopausal and postmenopausal patients .

P value =7.81 , x^2=13.7% , df=3

Table 4

Showed histopathological study

20(21.2%) showed atrophic endometrium (histopathologically revealed tissue insufficient for diagnosis and this reflect atrophic endometrium) , 6(6.3%) patients were premenopausal and 14(14.8%) postmenopausal patients .

42(44.6%) main bulk of patients showed non secretory endometrium (proliferative).

Histopathological studies showed no cases of endometrial carcinoma

16(16.9%) showed endometrial hyperplasia , 6(6.3%) patients were premenopausal and 10(10.6%) were postmenopausal patients

2 out of 10 postmenopausal patients did total abdominal hysterectomy due to atypical hyperplasia.

Statistically this table showed no difference in risk of hyperplasia between premenopausal and postmenopausal patients

P value =9.49 , x^2=8.65, df= 4

Table 1 patients characteristic

	No.	percentage
Age		
≤ 40	26	27.08%
41-50	18	18.75%
51-60	44	45.8%
≥ 61	8	8.3%
Menopausal state		
Premenopausal	44	45.8%
postmenopausal	52	54.1%
Stage of breast cancer	40	41.6%
Early		
advanced	56	58.3%

Table 2 patient's symptoms

Symptoms	premenopausal		postmenopausal		total	
	No.	%	No.	%	No.	%
Abnormal vaginal bleeding and menorrhagia	24	25%	42	43.7%	66	68.7%
Vaginal discharge	14	14.5%	8	8.3%	22	22.8%
Pain	6	6.2%	2	2.08%	8	8.28%
total	44	45.7%	52		96	

X^2= 0.241 , df = 2 , p value = 5.99

Table 3 ultrasound findings

USS	Premenopausal		Postmenopausal		total	
	No.	%	No.	%	No.	%
Less than 6mm	10	10.4%	12	12.5%	22	22.9%
7-9	17	17.7%	7	7.2%	24	24.9%
≥1cm	13	13.5%	27	28.1%	40	41.6%
Others Fibroid ,polyp	7	7.2%	3	3.1%	10	10.3%
total	47		49		96	

X^2= 13.7 , df = 3 , p value = 7.81

Table 4 histopathological findings

Histopathological findings	premenopausal		postmenopausal		total	
	No.	%	No.	%	No.	%
Atrophic	6	6.3%	14	14.8%	20	21.2%
Secretory	5	5.3%	3	3.1%	8	8.5%
Non secretory	22	23.4%	20	21.2%	42	44.6%
Combine	5	5.3%	3	3.1%	8	8.5%
Endometrial hyperplasia, endometrial carcinoma	6	6.3%	10	10.6%	16	16.9%
total	44		50		94	

$X^2 = 8.652$, df = 4 , p value = 9.49

more)the more risk and the more the dose (more than 40mg/day)the more the risk ([7]) magriples etal

The main presenting symptoms in our study was abnormal vaginal bleeding and discharge and this in agreement with all studies done (1,2,3,4,5, 6, 7,…..).

Ultrasound provide non invasive mean of screening of endometrium in breast cancer treated patients.

Lahti etal,([8]) reported cutoff value 5mm to define abnormal endometrium while Kadar etal([9]) , reported 100% value of atypical endometrial hyperplasia if endometrial strip ≥ 8mmin breast cancer postmenopausal patients treated with tamoxifen

In our study there were no statistical difference between premenopausal and postmenopausal patients in ultrasound findings and this in disagreement with kadar etal, study and in agreement with (Gerber

Discussion

Though tamoxifen has a potential role as chemopreventive agent in treatment of patients with breast cancers ,still its uses associated with a lot of side effects like endometrial carcinoma and others premalignant endometrial changes

These side effects varied substantially between studies done.

Tamoxifen side effects depends on duration of uses , the longer the duration (5 years and etal.,)([10]) study which confirm poor predictive value of ultrasound to assess the endometrial thickness , thickness dose not necessarily correlates with specific pathological endometrial changes , as stromal edema and stromal hypertrophy were one of tamoxifen side effects.([11])

The Incidence of endometrial polyps also high in breast cancer treated patients with tamoxifen 8-36% ([12]),([13]) still its rate is low in our both studied groups

A review of Assikis etal., ([14])estimated that tamoxifen had 3 fold increase in proliferation of endometrium and polyps formations compared to controls , this in agreement with our study which showed bulk of histopathological findings (42%) had proliferative endometrium

In spite of increasing risk of endometrial hyperplasia especially in postmenopausal patients which accounted for 1.3-20% ,([15]),while in premenopausal patients still varied and unproven ([16]) ,our study showed no significant difference in risk of hyperplasia between premenopausal and postmenopausal patients.

our study did not confirm any increase in risk of endometrial carcinoma in both studied group premenopausal and postmenopausal which can be explained by smaller prophylactic dose of tamoxifen used and the shorter duration (2years).

Recommendation

To increase effectiveness of study , symptomatic studied group should be assessed by hysteroscopy and hysteroscopically directed endometrial biopsy with larger sample size and duration more than two years .

References

1 .Neven P, Vergote I . Should tamoxifenusersbe screened for endometrial lesions ? Lancet 1998;351:155-7.

2 .BarakatRR ,etal., Tamoxifen and endometrial neoplasia . Clinic obstet.gyneco. 1996;39:629-40.

3 . Machado F, Rodriguez JR , Leon JP ,etal,.Tamoxifen and endometrial carcinoma . is screening necessary? A reveiwof literatures .Eur .journalgyneco. Oncol. 2005; 26 :257-65 .

4 . Sandra A .Polin, Susan M.Ascher .A review : the effect of tamoxifen on genital tract. International cancer imaging society 2008; 8: 135-145.

5 . Cohen I ,etal., endometrial pathologies associated with postmenopausal tamoxifen treated breast cancer patients . Gyneco.Oncol. 2004; 94 : 256 – 66 .

6 . Cheng WF, Lin HH , Torng PL, Huang SC .Comparison of endometrial changes among symptomatic tamoxifen treated and non treated premenopausal and postmenopausal breast cancer patients . Gyne.Oncol. 1997; 66:233-7 .

7 .Magriples U, Naftolin F, Schwartz PE , etal., High grade endometrial carcinoma in tamoxifen treated breast cancer patients . J. Clin. Oncol.1993 ;11:485-90 .

Lahti E, Blanco G, kanppila A , etal,. Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen .Obstet.Gynecol. 1993; 81:660-4 .

9 . Kedar etal,. Effect of tamoxifen on uterus and ovaries of postmenopausal women in randomized breast cancer prevention trial.
Lancet (1994) ;343:1318-1321 .

10 .. Gerber B, Krause A, Muller H ,etal, . Effect of adjuvant tamoxifen on endometrium in postmenopausal women with breast cancer :a prospective long term study . J Clinc.Oncol 2000; 18:3464-70 .

11 .Ascher SM, Imoak I , Lage JM . Tamoxifen induced uterine abnormalities: the role of images .Radiology 2000; 214:29-38 .

12 .S.Gupta, V.R.Tandon ,B.Kapoor , A.Gupta,V.Kajuria,G.D.Gupta .the effect of tamoxifen therapy on the endometrium of postmenopausal patients of breast cancer. Indian J.Pharmacol. Aug. 2006; vol38,issue 4, 289-290.

13 .Schlesinger C, Kamoi S , Ascher SM , etal,. Endometrial polyps : a comparison study of patients receiving tamoxifen with two control groups . Int .J . Gynecol. Pathol 1998; 17:302-11.

14 .Assikis VJ, Jordan VC :Gynecological effects of tamoxifen and the association with endometrial carcinoma . Inter. J. GynecolObstet .1995; 49:241-257.

15 .BarakatRR ,GilewiskiTA,Almadrones , etal,. Effect of adjuvant tamoxifen therapy on endometrium in women with breast cancer : Aprospective study using office endometrial biopsy. Jour. Clin. Oncol 2000 ,vol . 18, no. 20 ,pp 3459-3463 .

16 .Juneta M, Jose R, KekreAN ,Niswanatha F , ETAL,. Tamoxifen induced endometrial changes in postmenopausal women with breast cancer .Int. J. Gynecol. Obstet. 2002; 76:279-84.