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ROLE OF LOW DOSE OF MIFEPRISTONE IN MANAGEMENT OF FIBROID IN PERIMENOPAUSAL WOMEN: A COMPARATIVE STUDY.

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Abstract

Introduction: Uterine leiomyoma is the commonest benign gynaecological tumour occurring in upto20% to 80% of women reaching perimenopausal stage and 40% has symptoms severe enough to warrant therapy. Recent evidence suggests that progesterone is essential for maintenance and growth of uterine leiomyoma and that estrogen is required only for upregulation of progesterone receptors. Mifepristone is synthetic steroid, derived from norethindrone, progesterone receptor modulator with primarily antagonistic property. The present study aimed to evaluate the efficacy and safety of low dose of mifepristone in medical management of uterine leiomyoma

Materials and methods: the study is being conducted in obstetrics and gynecology department of PMCH. In 2 years, 100 patients with age between 40-50 years with multiple or single fibroid with symptoms requiring treatment with normal blood biochemistry profile were studied. Two groups were made, each of 50 patients. Group I was given mifepristone in dose of 25mg/day; and Group II was given mifepristone in dose of 10mg/day for 3 months. Patients were followed up at 3 months and 6 months of starting treatment.

Results: In both groups, there was decrease in size of fibroid, control of bleeding, improvement of symptoms and hemoglobin profile.

Conclusion: Low dose of mifepristone is useful for decreasing the size of fibroid, control of bleeding, improvement of hemoglobin profile and for medical management of fibroid.

Keywords: mifepristone, fibroid, management

Introduction

Myomas are the most frequently recorded benign smooth muscle tumor of the uterus, affecting 20%–60% of women of reproductive age.[1] At present, although there are a lot of research about the prevention and treatment of uterine fibroids, the etiopatogenesis of uterine fibroids is still unclear. The incidence of fibroids in pregnancy reported ranges from 0.1 to 10.7% of all pregnancies and increases as the female chooses to postpone pregnancy later on.[2] It was found that 10%–40% of prepartum complications which happened in pregnancy with fibroid have been associated with the presence of it.[3] Also, they are related to a lot of antepartum, intrapartum, and postpartum complications.[4]

There are conflicting data on the relationship between obstetric outcomes and uterine fibroids, and the mechanism by which fibroids influence obstetric outcomes is unclear. Some studies have shown a relationship between uterine fibroids and pregnancy complications, such as preterm birth, premature rupture of membranes (PROM), fetal malpresentation, placental abruption and intrauterine fetal demise.[5-7]

Recent studies have provided the evidence that progesterone has a critical role in Leiomyoma growth. This leads to introduction of antiprogestins for the treatment of fibroid. Mifepristone competitively binds and inhibits progesterone receptors. It significantly reduces fibroid volume, menorrhagia, dysmenorrhoea, and pelvic pressure symptoms. Studies have been done with doses ranging from 5-50mg/day for 3-6months. Reduction in size of fibroid, amenorrhoea and improvement of haemoglobin level avoids blood transfusion prior to or during surgery.[8]

Reduction in fibroid size also technically simplifies the operative procedures, an abdominal hysterectomy could be converted into a vaginal procedure and vertical incision could be converted into a transverse incision. The decrease in leiomyoma volume and improvement in symptoms are comparable to GnRH analogues but mifepristone is well tolerated due to minimal side effects as mild atypical hot flushes, nausea with no reduction in bone mineral density after treatment.[9]

This study wass done at PMCH to determine the effects of low dose of mifepristone on uterine and fibroid volume reduction, improvement in symptoms & its adverse effect in perimenopausal women.

Materials and Methods

This study was done in 100 patients attending Obstetrics & Gynaecology OPD of PMCH, in which 25mg mifepristone was given in 50 patients (Group I) and 10 mg mifepristone was given in 50 patients (Group II) daily for 3 months. Patients were followed up at 3 months and 6 months of starting treatment.

Inclusion and exclusion criteria

Women between 40-50 years of age with single or multiple fibroids were included consecutively in the study if they were symptomatic (menorrhagia, dysmenorrhoea, abdominal lump, dull aching lower abdominal pain, dyspareunia) or if the largest fibroid was >5 cm on ultrasound. Ultrasound pelvis was done for all patients to exclude any other obvious causes like adenomyosis, endometriosis, adnexal mass for the above symptoms.

Exclusion criteria remained more than 20 wk gravid size uterus, fibroids >15 cm by ultrasound, grade-0 submucosal fibroids, renal or hepatic dysfunction, suspected adenomyosis, current genital infection, endometrial hyperplasia with atypia and hormonal medication (Progestogens/ GnRH) within 3 months and women desiring pregnancy.

Methodology

Demographic and baseline clinical profile including details of menstrual cycle, symptoms and their severity was noted. Patients were followed up at 1 and 3 months while on therapy and then at 6 months *i.e*. 3 months after stopping therapy to look for recurrence of symptoms or regrowth of fibroid. On each visit clinical symptoms including bleeding and spotting, PBAC score, VAS score and any side effects were assessed. Amenorrhoea was defined as the absence of bleeding for two consecutive cycles. Ultrasound was done to determine the number of myoma and endometrial thickness.

Statistical analysis

Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2. EPI INFO is a trademark of the Centers for Disease Control and Prevention (CDC). Using this software, basic cross-tabulation, inferences and associations were performed. Chi-square test was used to test the association of different study variables with the study groups. Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions. T-test was used to compare the means. One way analysis of variance (ANOVA) was used to compare more than two means at a time and also Tukeys test followed by one way ANOVA was used to calculate critical difference (CD) to compare the means pair wise. P< 0.05 was considered statistically significant.

Results

Table 1: Clinico-demographic profile of the study population

Variables	Mean±SD	
	Mifepristone-25 mg (n=50)	Mifepristone-10 mg (n=50)
Age (in years)	45.06±2.71	43.70±2.41
Parity	3.06±1.04	3.36±1.05
BMI	24.36±1.90	24.67±1.73

Table 2: Comparison of fibroid volume of the patients of the two groups at different time interval

Descriptive Statistics	Fibroid Volume at Base Line	Fibroid Volume at 3 months	Fibroid Volume at 6 months	F-value ($F_{2, 147}$)	p-value
Mifepristone-25 mg (n=50)					
Mean±s.d.	139.92±15.13	90.95±9.83	103.54±11.19	215.23	<0.0001 S
Mifepristone-10 mg (n=50)					
Mean±s.d.	137.32±15.15	107.11±11.82	128.39±14.17	63.37	<0.0001 S
p-value	0.39 NS	0.08 NS	0.11 NS		

NS-Statistically not significant
S-Statistically significant

Table 3: Comparison of Menstrual Blood Loss of the patients of the two groups at baseline

Menstrual Blood Loss	Baseline		At 3 months		At 6 months	
	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)
0	0(0.0%)	0(0.0%)	48(96.0%)	46(92.0%)	44(88.0%)	42(84.0%)
1	0(0.0%)	0(0.0%)	1(2.0%)	2(4.0%)	3(6.0%)	5(10.0%)
2	0(0.0%)	0(0.0%)	1(2.0%)	1(2.0%)	2(4.0%)	2(4.0%)
3	4(8.0%)	3(6.0%)	0(0.0%)	1(2.0%)	0(0.0%)	0(0.0%)
4	46(92.0%)	47(94.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
TOTAL	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)
Chi-square (χ^2)	0.15		1.51		0.54	
p-value	0.84 NS		0.26 NS		0.36 NS	

Table 4: Comparison of dysmenorrhea of the patients of the two groups at baseline

Dysmenorrhoea	Baseline		At 3 months		At 6 months	
	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)
0	0(0.0%)	0(0.0%)	40(80.0%)	39(78.0%)	37(74.0%)	36(72.0%)
1	2(4.0%)	3(6.0%)	6(12.0%)	6(12.0%)	7(14.0%)	7(14.0%)
2	19(38.0%)	17(34.0%)	4(8.0%)	5(10.0%)	5(10.0%)	6(12.0%)
3	29(58.0%)	30(60.0%)	0(0.0%)	0(0.0%)	1(2.0%)	1(2.0%)
TOTAL	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)
Chi-square (χ^2)	3.08		0.12		0.002	
p-value	0.31 NS		0.99 NS		0.99 NS	

Table 5: Comparison of pelvic pain of the patients of the two groups at baseline

Severity of Pelvic pain	Baseline		At 3 months		At 6 months	
	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)	Mifepristone 25 mg (n=50)	Mifepristone 10 mg (n=50)
Severe	3(6.0%)	4(8.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Moderate	5(10.0%)	5(10.0%)	1(2.0%)	2(4.0%)	2(4.0%)	2(4.0%)
Mild	7(14.0%)	8(16.0%)	1(2.0%)	1(2.0%)	1(2.0%)	2(4.0%)
None	35(70.0%)	33(66.0%)	48(96.0%)	47(94.0%)	47(94.0%)	46(92.0%)
TOTAL	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)	50(100.0%)
Chi-square (χ^2)	4.60		0.06		0.48	
p-value	0.26 NS		0.93 NS		0.37 NS	

Table 6: Comparison of endometrial thickness (in mm) of the patients of the two groups at different time interval

Descriptive Statistics	Endometrial thicknessat Base Line	Endometrial thicknessat 3 months	Endometrial thicknessat 6 months	F-value ($F_{2, 147}$)	p-value
Mifepristone-25 mg (n=50)					
Mean±s.d.	6.38±1.38	7.48±1.46	5.46±1.06	25.31	<0.0001 S
Mifepristone-10 mg (n=50)					
Mean±s.d.	6.50±1.27	7.34±1.59	5.36±1.16	31.39	<0.0001 S
p-value	0.65 NS	0.64 NS	0.67 NS		

Discussion

Recent studies have shown that mifepristone treatment reduced the prevalence and severity of dysmenorrhea, menorrhagia, and pelvic pressure and also reduced the size of fibroid and also improves haemoglobin profile. The first study demonstrating the decrease in leiomyoma volume in response to progesterone antagonist was conducted by Murphy et al.[10] Several other clinical trials using mifepristone in doses of 5-50 mg were conducted for varying periods between 3 to 12 months.[11-14] The exact dose and duration of the drug is yet to be determined by conducting trials in different doses and for different duration.

Mean age of patients in group I and group II was 45.06 years and 43.70 years respectively, in which all patients were in 40 to 50 years age group Mean parity of group 1 was 3.06+/-1.04 and mean parity of second group was 3.36+/-1.05.The range of parity in both groups was same from 2-6. Thus, the baseline parity of both groups were same. It was comparable to study done by Madhu Bagaria et al.[15], in which most patients were para 3 or above.

In the present investigation the percentage decrease in fibroid volume at 3 months was group I was 34.99% and in group II, it was 21.99%.At the follow up at 6 months, the size of fibroid increased in both groups but it did not reach the baseline. The decrease in size of fibroid was more with 25mg dose. Similarly Vidushi kulshreshtha et al.[16] found 35.7% decrease in size of fibroid at 3 month (on 25 mg mifepristone) and 22.5% reduction in fibroid size at 3 month in group II (10mg mifepristone). They also found that 35% reduction in fibroid volume at 3 month and 26.5% reduction in fibroid volume at 6 months with 2.5mg of mifepristone given daily for 3 months

Our study revealed that at the end of 3 months, 80% patients in group I (25mg) and 78% patients in group II (10mg) completely got relief of dysmenorrhea. At the end of 6 months, 74% patients in group I (25mg) and 72% patients in group II (10mg) got complete relief of dysmenorrhea. Similarly Madhu Bagaria et al.[15] also found that 80% of patients relieved completely of dysmenorrhea after 3 months on therapy of 10mg mifepristone.

In group I (25 mg mifepristone), 30% patients had pelvic pain, 96% patients got relief at 3 months and 94% patients got relief at 6 months. While in Group II (10 mg), 34% patients complained of pelvic pain. 94% patients got relief at 3 months and 92% patients got relief at 6 months. Therefore, both doses had significantly same relief from the symptom of pelvic pain. While Yang et al.[12] and Zeng et al.[17] found 100% relief of pelvic pain after 3 month of therapy. Carbonell et al.[18] found that most patients got relief of pelvic pain.

Conclusion

Our study concluded that low dose of mifepristone led to symptomatic relief in patients with myoma with more than 90 percent reduction in menstrual blood loss. It also caused relief of dysmenorrhea and pressure symptoms due to decrease in size of fibroid. The effect of 25mg mifepristone was better than the 10 mg dose in reduction of the size of fibroid, but the symptomatic relief of both doses was more and less same. Low dose of mifepristone can be a reasonable choice in perimenopausal women in whom myoma would regress after menopause. Although it's use as a primary medical therapy is limited due to recurrence after stopping treatment, it can be used as preoperative adjunct, especially in patients with preoperative severe anaemia, large fibroid (where surgery is technically difficult or where leiomyoma are unresectable).

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