

Comparison of ormeloxifen and mifepristone in management of leiomyoma uterus

Madhulika Singh^{1*}, Amrita Chourasia², Shalini Singh³, Nidhi Sachan⁴

¹Junior Resident, ²Associate Professor, ^{3,4}Lecturer, ¹⁻⁴Dept. of Obstetrics and Gynaecology, ¹⁻⁴Moti Lal Nehru Medical College, Allahabad, Uttar Pradesh, India

*Corresponding Author: Madhulika Singh

Email: drmadhulikasingh86@gmail.com

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Abstract

Aims and Objectives: To compare the effect of mifepristone and ormeloxifen on symptomatology, size and vascularity of fibroid and also to compare the compliance and side effects of both these drugs.

Materials and Methods: This study was conducted in the department of obstetrics and gynecology at Swaroop Rani Nehru hospital, Allahabad and Kamla Nehru memorial hospital, Allahabad over a period of one year between 2016-2017 in 90 fibroid patients who gave consent for the study. Depending on their choice they were randomly divided into 2 groups. Group A included 44 fibroid patients who were given mifepristone and Group B included 46 fibroid patients were given ormeloxifen. Assessment of heavy menstrual bleeding by pictorial blood loss assessment chart, dysmenorrhea and dyspareunia by visual analogue scale, estimation of hemoglobin and repeat imaging to assess size, number, endometrial thickness, Doppler velocimetry of fibroid was done and all variables were compared in relation to pretreatment and post-treatment parameters by using chi square test.

Results: 97.7% patients in group A and 95.6% patients in group B were compliant towards treatment. A significant reduction in HMB (group A-51.16% to 18.6% \$ group B-45.45% to 20.45%), mean pbac score (group A-246.6 to 65.2; p<0.0001 \$ group B-242.4 to 66.5; p<0.0001) and mean VAS (group A-7.5±2.6 to 2.0±0.6 \$ group B-7.0±2.1 to 1.8 0.3) was found with significant rise in Hb level (grp A-9.6 1.5 to 12.4 1.2; p<0.001 \$ grp B-10.0 1.8 to 12.6 1.6; p<0.001) during 6 months follow up. On USG a significant reduction in size of fibroid was found with mifepristone (p<0.0001) as compared to ormeloxifen (p<0.624) while significant reduction in vascularity was noted with both of them (Group A-p<0.001, Group B-p<0.001). Significant endometrial hyperplasia noted with mifepristone (p<0.0001) while significant reduction with ormeloxifen (p<0.0001)

Conclusion: Mifepristone and ormeloxifen were equally effective for symptomatic relief in fibroid patients. Myoma size was significantly reduced by mifepristone only, with notable endometrial hyperplasia whereas ormeloxifen causes significant reduction in endometrial thickness. No major side effects observed with any of them.

Keywords: Mifepristone, Ormeloxifen, Leiomyoma, SERM, PBAC score.

Introduction

Uterine fibroid is a common concern due to associated heavy menstrual bleeding and anemia negatively affecting women's life. The prevalence of uterine fibroid in India is upto 20-30% in reproductive females¹ and 10-20% of infertility is attributed to uterine fibroid^{2,3} thus it becomes a major socioeconomic health burden to the society. Though surgical treatment still remains the mainstay of the treatment, medical methods had evolved over the years with the advent of many effective oral drugs. Growing evidences indicate that progesterone and estrogen receptor play key role in uterine leiomyoma development and growth.⁴ Progesterone causes suppressed apoptosis and stimulates proliferation of the leiomyomatous smooth muscles.⁵⁻⁷ Whereas estrogen indirectly stimulates leiomyoma growth by up-regulating the progesterone receptors. Progesterone and estrogens also affect leiomyomatous growth by up regulation of EGF (epidermal growth factor) which increases estrogen and hence progesterone receptors¹² and VEGF which increases fibroid vascularity.^{14,15} An antiprogesterone and antiestrogenic medication will antagonize progesterone and estrogenic action on fibroid and will help in reducing its size. Over the years the continued search had led to the development of such magic bullet fulfilling the maximum criteria of "Ideal Tablet" that

can be given orally in least frequent dosing with minimal side effects has evolved antiprogesterone mifepristone and antiestrogen ormeloxifen.

Material and Method

Type of Study

Interventional

Place of Study

Department of Obstetric and Gynaecology at Swaroop Rani Nehru hospital, Allahabad and Kamala Nehru Memorial hospital, Allahabad over a period of one year; 2016-2017.

Sampling Methods

Incidental sampling

Inclusion Criteria

All symptomatic or asymptomatic patients of uterine leiomyoma aged 20-50 yrs. Asymptomatic patients with incidental diagnosis of fibroid uterus in imaging were enrolled in the study with the purpose to see the effect of these drugs on size and vascularity of uterine fibroid

Exclusion Criteria

Big fibroids (size more than 15 cm by ultrasonography), uterine size more than 20 weeks, coexisting adenomyosis, endometriosis and adnexal masses, malignancies of uterus/cervix/ovary/vagina/endometrial hyperplasia with atypia, hormonal medication within 3 months, medical diseases like – liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism, platelet disorders or coagulopathy, hypersensitivity to the drug and very severe anaemia <6gm/dl, non consenting patients.

Sample Collection

90 patients with fibroid uterus were interrogated and examined thoroughly and then were divided into two arbitrary groups (A & B) on the basis of their choice of drug; mifepristone or ormeloxifene.

Intervention

Group A included 44 women who took mifepristone 10 mg once daily for six months.

Group B included 46 women who took ormeloxifen 60 mg twice weekly for six months.

Follow ups

The follow-ups were done at 3 and 6 monthly intervals. The parameters assessed were amount of menstrual blood loss (Pictorial blood loss assessment chart; abnormal PBAC score ≥100), dysmenorrhea (Visual analogue scale; abnormal scale >3), pressure symptom, ultrasonographic assessments of size & number of fibroid, endometrial thickness, uterine vascularity through Doppler velocimetry and adverse effect.

Statistical Analysis

The statistical significances were measured by calculating P value (P value < 0.05)

Results

Table 1: Mean age of women in group A & Group B were 40.8 ± 6.8 and 41.2 ± 7 respectively. In both the groups maximum numbers of patients were from urban background; 76.7% and 90.9%, belonged to middle class; 65.1% and 61.4%, were married; 88.4% and 95.5% with parity three; 32.55% and 36.36% in group A and group B respectively.

Table 2: Heavy menstrual bleeding without dysmenorrhea was the most common symptom; 50% followed by HMB with dysmenorrhoea; 27.3% followed by pressure symptoms; 3.5%.

In Group A at 3 & 6 months of followup reduction in HMB without dysmenorrhea were statistically significant; 23.3% (p<0.005) & 6.9% (p<0.001) and in group B 25% (0.005) & 6.8% (p<0.001) whereas HMB with dysmenorrhea had significant improvement only at 3 month followup; 9.3% (p<0.005) in group A and 6.8% (p<0.005) in group B. No significant improvement observed at 6 months followup. Pressure symptoms had not improved at all in both the groups at both 3&6 months follow up. On comparing both the drugs the effect on HMB without dysmenorrhea, HMB with dysmenorrhea and pressure symptoms were found to be comparable with no statistically significant difference (p>0.005)

Table 1: Socio Demographic profile of participants

Variables	Frequency (%)	
	Group A (N=43)	Group B (N=44)
Mean age± SD	40.8 ±6.8	41.2±7.0
Residence	Frequency(%)	Frequency(%)
Urban	33(76.7%)	40(90.9%)
Rural	10(23.3%)	4(9.1%)
Socio economic status	Frequency(%)	Frequency(%)
Upper	5(11.6%)	4(9.1%)
Middle	28(65.1%)	27(61.4%)
Lower	10(23.2%)	13(29.5%)
Marital status	Frequency(%)	Frequency(%)
Unmarried	5(11.6%)	2(4.6%)
Married	38(88.4%)	42(95.5%)
Parity	Frequency (%)	Frequency (%)
P0	5(11.62%)	3(6.8%)
P1	6(13.95%)	6(13.6%)
P2	8(18.60%)	7(15.9%)
P3	14(32.55%)	16(36.3%)
>P3	10(23.25%)	12(27.2%)

Table 2: Symptomatology profile at baseline and response at 3 months and 6 months

Clinical Features	Time period	Group A (mifepristone) Frequency (%) (p-value)	Group B(ormeloxifen) Frequency (%) (p-value)	Total Patients Frequency (%)	P Value (group A vs group B)
HMB without dysmenorrhea	Baseline	22 (51.2%)	20 (45.5%)	42(50%)	P=0.826
	3 months	10 (23.3%); P<0.005	11 (25.0%); P<0.005		P=0.629
	6 months	3 (6.9%); P<0.001	3 (6.8%); P<0.001		P=0.782
HMB with dysmenorrhea	Baseline	11 (25.6%)	12 (27.3%)	23(27.3%)	P=0.086
	3 months	4 (9.3%); P<0.005	3(6.8%); P<0.005		P=0.829
	6 months	4 (9.3%); P=0.072	2 (4.5%); P=0.761		P=0.761
Pressure symptoms	Baseline	2 (4.7%)	1 (2.3%)	3(3.5%)	P=0.822
	3 months	2 (4.7%); P=0.821	1(2.3%); P=0.732		P=0.062
	6 months	2 (4.7%); P=0.868	1 (2.3%); P=0.788		P=0.266

Fig. 1,2 & 3: The baseline mean PBAC score was 246.65±9.14 and 242.43±12.9; Mean VAS Score- 7.5±1.4 and 7.05±1.7; Mean ET- 7.48±1.4 and 7.84±1.6 in group A and group B respectively. At 3 months, significant reduction was noticed in mean PBAC score; 130.56±5.7 (p<0.0001), 132.38±5.61 (p<0.0001); mean VAS score 2.66±0.4 (p<0.009), 2.5±0.6 (p<0.0001) in group A and group B respectively.

At 6 months followup significant improvement continued in mean PBAC score; 65.23±4.08 (p<0.0001), 66.57±3.81 (p<0.0001) in both group A and B respectively but mean VAS Score showed insignificant difference (p<0.216), (p<0.312) in both the drugs. The efficacy of both the drugs in relation to mean PBAC Score & VAS Score were comparable (p>0.001) Mean ET was reduced to 5.76 ± 3.18 (P<0.0001) and 3.47 ± 1.40 (p<0.0001) in group A at 3rd and 6th month followup. In contrast group B showed increase in mean ET; 7.87 ± 1.7 that was initially insignificant (P value=0.065) but became significant 9.41 ± 0.87 (p<0.0001) at 6 month.

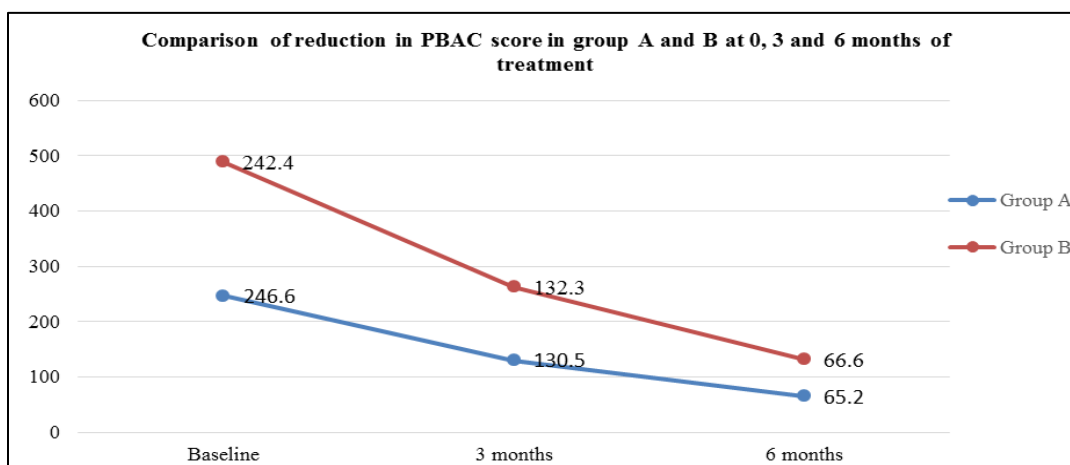


Fig. 1: Mean PBAC score at baseline, 3 months and 6 months of treatment

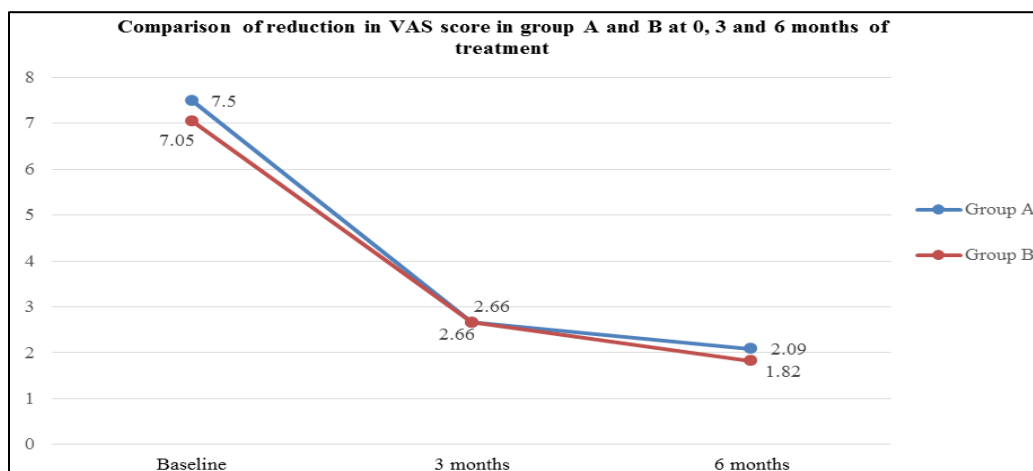


Fig. 2: Mean VAS score at baseline, 3 months and 6 months of treatment

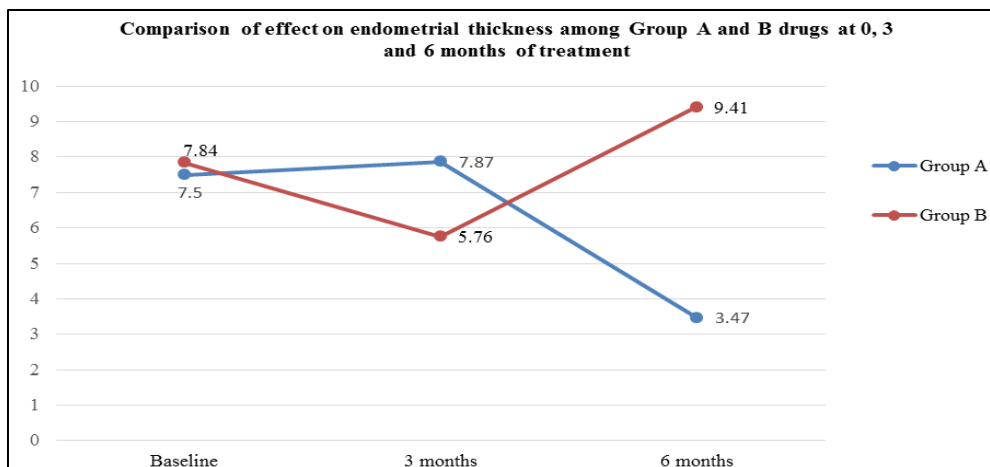


Fig. 3: Comparison of effect on mean endometrial thickness

Table 3: Baseline mean fibroid size along with Doppler flow Velocimetry were comparable in both the groups ($p < 0.312$; $p < 0.870, 0.450$).

In Group A significant reduction was found in size of fibroid at both 3 and 6 month; 4.0 ± 2.4 ($p < 0.005$), 3.0 ± 2.1 ($p < 0.001$) respectively, along with significant improvement in PI and RI; 0.88 ± 0.24 ($p < 0.044$); 0.59 ± 0.24 ($p < 0.043$) and 0.97 ± 0.19 ($p < 0.001$); 0.65 ± 0.19 ($p < 0.05$) at 3 and 6 month respectively.

Group B showed no significant reduction in size of fibroid both at 3 & 6 month; 5.3 ± 2.2 ($p = 0.214$), 4.8 ± 1.8 ($p = 0.624$) but reduced vascularity with improvement in PI and RI values were noticed at 3 month; 0.90 ± 0.24 ($p < 0.006$); 0.6 ± 0.18 ($P < 0.04$) and 6 months; 0.98 ± 0.17 ($p < 0.05$) 0.68 ± 0.14 ($p < 0.03$) followup.

On comparing both the groups the fibroid size was significantly more reduced in Group A in comparison to Group B ($p < 0.005$; $p < 0.001$) but improvement in vascularity were found to be comparable both at 3 & 6 month ($p = 0.845, 0.764$; $p = 0.812, 0.450$)

Table 4: No serious adverse effects were noted in both groups. The most worrisome side effect was infrequent menstruation, more commonly associated with ormeloxifen than mifepristone; 61% Vs. 55.8%.

Table 3: Mean Fibroid size, Doppler velocimetry at baseline, 3 months and 6 months among the study population

	Group A Mean±S.D (p-value)	Group B Mean±S.D (p value)	p Value(Group A vs Group B)
Fibroid Size			
Baseline	6.2±1.8	5.8 ±2.0	0.312
3 months	4.0 ±2.4; p<0.005	5.3 ±2.2; p=0.214	<0.005
6 months	3.0 ±2.1; p<0.001	4.8 ±1.8; p=0.624	<0.001
Doppler velocimetry			
Baseline			
PI*	0.78 ±0.23	0.77 ±0.18	0.870
RI#	0.50 ±0.23	0.51 ±0.24	0.450
3 months			
PI	0.88 ±0.24 p=0.044	0.90 ±0.24; p=0.006	0.845
RI	0.59 ±0.24; p=0.043	0.60 ±0.18; p=0.04	0.764
6 months			
PI	0.97 ±0.19; p<0.001	0.98 ±0.17; p<0.05	0.812
RI	0.65 ±0.19; p<0.05	0.68 ±0.14; p<0.03	0.450

*PI: Pulsatility index, #RI: resistivity index

Table 3: Side effects due to the two drugs among the patients

Side Effects	Group A Frequency (%)	Group B Frequency (%)	p value
Nausea and vomiting	3 (7.0%)	1 (2.3%)	0.462
Headache	2 (4.7%)	1 (2.3%)	0.824
Abdominal pain	5 (11.7%)	2 (4.5%)	0.628
Amenorrhea	2 (4.7%)	3 (6.8%)	0.092
Infrequent menses	24 (55.8%)	27 (61.4%)	0.088

Discussion

Our study demonstrates that the self-reported prevalence of uterine fibroids was highest in fourth decade that is very similar and consistent with other studies like Anne Zimmermann et al; 2012 in Germany⁸ and H. Eisinger et al; 2009 in Meldrum⁹ who also found highest prevalence in the age groups ranging between 41-49 years.¹⁰ Although the inverse association between myoma risk and parity is well known⁵⁻⁷ the noncomparable findings of getting myomas in women with multiparity may be explained by strong social practice of mandatory marriage and early child bearing in the initial years of marriage only. So by the time myoma tends to grow in the uterus, the women already had pregnancy and child bearing. The most common presenting complaint has been documented to be HMB and dysmenorrhea³⁰ as found in this study also.

Mifepristone caused reduction in the menstrual blood loss, fibroid size and vascularity by its antiprogesterone effect thus rendering progesterone induced activities like increased VEGF^{14,15} increased EGF, increased leiomyomatous cell proliferation.

Relief in dysmenorrhea is due to reduced production of prostaglandins, Vasopressin and endothelin induced spasmodic uterine contractions^{18,19} Significant improvement in dysmenorrhea was found in initial months that plateaued after 3 months depicts obvious pain relief from distressing pain visible on the VAS Scale that reduced to less, to be noticed in later months.

The same findings had been explained by Alka Kriplani et al, 2009, New Delhi¹⁶ and Vidushi Kulshrestha et al, 2013, New Delhi¹⁷ and Dasgupta M, et al, 2016, in West Bengal.²⁰

Though mifepristone caused reduced menstrual blood loss, fibroid size and vascularity, the ET was increased both at 3 & 6 months as has also been shown by Dhananjay BS et al, 2013, Pondicherry²⁶ (a significant increase in mean ET from 6.82±1.18 to 9.92±2.72;p<0.001). It blocks progesterone receptors which leads to unopposed action of estrogen on endometrium causing increased endometrial proliferation.^{13,14}

Moreover, mifepristone has been found to increase in plasma ACTH leading to rise in plasma cortisol and adrenal androgen. The peripheral aromatization of adrenal androgen to estradiol causes further increase in estrogen levels causing endometrial proliferation.¹³⁻¹⁴

Ormeloxifen reduced Mean PBAC Score, VAS Score, Vascularity and Endometrial thickness by antagonizing induced proliferation of endometrium¹⁵ and fibroid itself and decreased production of VEGF, EGF.

Ormeloxifen primarily antagonizes estrogenic action of endometrium only and not on myoma,³¹ thus had no effect on size of fibroid.

Similar results were also explained by Dasgupta, M, et al, 2016, in West Bengal Amenorrhea caused by both the drugs was counted as side effect rather we found it welcome by the patient to recover their anaemia and mental distress that was caused by HMB. The side effect profile included no major event, similar to the study conducted by Carbonell Esteve et al, 2008 Cuba and Sachita Karmakar et al, 2013 in Pune^{27,28}

Conclusion

Treatment of uterine fibroids by mifepristone or ormeloxifen was associated with reduction in menstrual blood loss and pain with equal efficacy. It was found that mifepristone reduced the size of fibroid more effectively while ormeloxifen had significant effect on endometrial thickness. We concluded from the study that both these drugs can be used for treatment of symptomatic fibroids with negligible side effects but mifepristone should be preferred over ormeloxifen if considerable reduction in fibroid size is desired.

Conflict of Interest: None.

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