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Comparative Study of Effect of Mifepristone (Antiprogesterone) and Ormeloxifene (SERM) on size of Uterine Leiomyoma and Uterine Artery Blood Flow

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Abstract

Introduction: Leiomyoma, commonly called as fibroid uterus is the most common neoplasm of the uterus. The term that emphasizes the origin of this tumour from smooth muscle cells and the predominance of these cells in the tumour.

Aims: This prospective randomised control study was to compare the efficacy of mifepristone (antiprogesterone) and ormiloxefene (SERM) in medical management of fibroid uterus in terms of change in size and volume of fibroid by ultrasonography and change in uterine artery blood flow by Color Doppler study of uterine artery.

Material and method: A prospective randomised control parallel group, open label clinical trial study was women in the age group of 30-50 years diagnosed with fibroid uterus diagnosed by ultrasonography, willing for medical management.Perimenopausal women with provisional diagnosis of fibroid with or without symptoms diagnosed clinically and confirmed by ultrasonography, irrespective of fertility status and having no medical contraindications were included for this study.

Result: Mean PSV and EDV in mifepristone group was 32.46±7.4 and 9.26±1.95 and in ormeloxifene group was 29.74±5.97 and 8.54±1.65 with p value 0.217 and 0.220 respectively. S/D ratio was similar in both the groups (3.5±0.23 & 3.49±0.18 in mifepristone and ormeloxifene respectively p=0.924). Baseline RI and PI in mifepristone were 0.71±0.01 and 1.62±0.25 compared to 0.71±0.01 and 1.6±0.23 in ormeloxifene group respectively (p value for RI and PI comparison between groups were 0.909 and 0.736).

Conclusion: Mifepristone can successfully reduce volume of uterine fibroid whereas, the effect of ormeloxifene on uterine fibroid are variable and may cause increase in size of uterine fibroid as in our study (>50%).

Keywords: Leiomyoma, mifepristone, ormiloxefene, and SERM.

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Introduction

Leiomyoma, commonly called as fibroid uterus is the most common neoplasm of the uterus. Various terms are used to describe this tumour viz. fibromyoma, leiomyofibroma, myoma, fibroma, leiomyoma, fibroid uterus. The last term, in spite of being most commonly used, probably is least accurate and hence, least acceptable.[1] The term leiomyoma, on the other hand, is rather a reasonably correct term that emphasizes the origin of this tumour from smooth muscle cells and the predominance of these cells in the tumour.[2]

Leiomyomas remain asymptomatic in at least 50% of affected women. However, in others, they may cause significantly poor quality of life though mortality is very rare. The clinical presentation has a wide range: abnormal menstrual bleeding including menorrhagia and intermenstrual bleeding; dysmenorrhoea and chronic pelvic pain unrelated to menstruation; sensation of heaviness in abdomen and aesthetically unacceptable abdominal enlargement; pressure symptoms such as a sensation of bloating; increased urinary frequency and bowel disturbance. In addition, they may compromise reproductive function by debatably contributing to subfertility, recurrent miscarriage and later pregnancy complications. Abnormal bleeding occurs in 30% of symptomatic women; this symptom along with bloating and pelvic discomfort due to mass effect constitutes the most common presentation of a symptomatic leiomyoma. The size, number and location of leiomyomas undoubtedly determine their clinical behaviour,but research is yet to correlate these parameters with clinical presentation.[3]

Fibroid is a steroid dependent tumour which has receptors for estrogen and progesterone. Therefore, antiprogesterone like mifepristone may induce regression of fibroid by withdrawal of progesterone action and/or by its interference with estrogen action. Most of the studies of mifepristone for the treatment of fibroid were small ranging in size between 14 to 75 subjects. The primary outcome of maximum studies was change in leiomyoma or change in uterine size. One of the studies measured the volume of uterus and largest leiomyoma.[4] Although the mechanism for fibroid size reduction with mifepristone is unclear, there is evidence that mifepristone decreases number of progesterone receptors in the myometrium and fibroids directly.

Ormeloxifene being the selective estrogen receptor modulator, is an estrogen antagonist on uterus and breast, it has mild estrogenic activity in vagina, bone, cardiovascular system and lipid profile without any progestational, androgenic or antiandrogenic property may reduce size of the fibroid and thus likely to reduce the symptoms related. Ormeloxifene has been successfully used in the treatment of Dysfunctional Uterine Bleeding, but its effect on fibroid uterus has not been evaluated.

Ultrasonography, by abdominal and/or transvaginal approach, remains the mainstay of pre-operative diagnostic confirmation of leiomyoma.[5] Studies have shown that for diagnosing leiomyomas, ultrasonography (USG) has 100% sensitivity and 99% specificity.[6] A uterine leiomyoma is a highly vascular neoplasm supplied by feeding vessels mostly entering from the periphery. Colour Doppler velocimetry of the uterine arteries have proved that the blood flow to the uterine artery/arteries increases significantly in leiomyomatous uterus;[7] the peak systolic velocity (PSV) increases and resistance index (RI) and pulsatility index (PI) fall. So changes in PSV and RI in uterine artery can be an effective indicator in assessing the response of fibroid to medical therapy with the mifepristone and ormeloxifene.

Aims And Objectives

AIMS: Main aim of this prospective randomised control study was to compare the efficacy of mifepristone (antiprogesterone) and ormiloxefene (SERM) in medical management of fibroid uterus in terms of change in size and volume of fibroid by ultrasonography and change in uterine artery blood flow by Color Doppler study of uterine artery.

OBJECTIVES: Following are the objectives of the study:

1. To compare change in size of fibroid after treatment with the study drugs by ultrasonography.

2. To observe change in the Peak Systolic Velocity (PSV), Resistance Index (RI) and Pulsatility Index (PI) of uterine arteries after treatment with the study drugs by Doppler.

3. To assess improvement or deterioration of subjective symptoms of patient.

Materials And Methods

Women in the age group of 30-50 years diagnosed with fibroid uterus diagnosed by ultrasonography, willing for medical management were enrolled from from March 2017 to August 2020. It was interventional prospective randomised control parallel group, open label clinical trial. This study enrolled 39 women (Mifepristone n=20 and Ormeloxifene n=19).

Samples were designed according to the following inclusion and exclusion criteria.

Inclusion criteria:

1. Age between 30-50 years.
2. Premenopausal at any phase of menstrual cycle and perimenopausal women.
3. Provisional diagnosis of fibroid with or without symptoms diagnosed clinically or by ultrasonography.
4. Irrespective of fertility status.
5. Physically fit enough for the study.

Exclusion criteria:

1. Pregnancy.
2. Women admitted for surgical treatment.
3. Those receiving GnRH analogue or danazol.
4. Postmenopausal women.
5. Age <30 years or >50 years.
6. Patients with degenerative changes in fibroid, adenomyosis, endometrial malignancy or polyp, cervical abnormality and DUB.
7. Hypersensitivity to drug.
8. Recent history of jaundice, renal disease PCOS, past and family history of thrombophlebitis.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.p-value ≤ 0.05 was considered for statistically significant.

Result And Discussion

This study was a prospective, randomised control parallel group open label study. Total number of patients recruited into the study was 52. 13 patients were lost to follow-up, 7 from ormeloxifene and 6 from mifepristone group. 39 patients completed the study, 19 received ormeloxifene and 20 mifepristone for the treatment of fibroid uterus for 3 months each.

Separate studies observed the effect of mifepristone on fibroid and ormeloxifene in DUB but no comparison on fibroids..

In our study, comparison of baseline characteristics like age, marital status, and parity did not show any significant difference between groups. Mean age in mifepristone group was 41.3±4.4 and in ormeloxifene group was 40±5.2 (p=0.422). All patients in ormeloxifene group were married whereas, 2 patients were unmarried in mifepristone group. Marital status though is not expected to change the possible outcome. Most of the patients in both the groups were multipara, 60%(12) and 79%(15) in mifepristone and ormeloxifene group respectively, p= 0.258.

Most common type of fibroid in both groups was intramural type, 60%(12) and 52.63%(10) in mifepristone and ormeloxifene groups respectively, p value being 0.910. At diagnosis, there was no significant difference in dimension and volume of fibroid and also in ultrasonographic variables on Color Doppler. Mean Volume of fibroid in mifepristone group was higher than in ormeloxifene group though p value was notsignificant. (81.7±27.5 vs 71.86±26.5 and p=0.262)

Mean PSV and EDV in mifepristone group was 32.46±7.4 and 9.26±1.95 and in ormeloxifene group was 29.74±5.97 and 8.54±1.65 with p value 0.217 and 0.220 respectively. S/D ratio was similar in both the groups (3.5±0.23 & 3.49±0.18 in mifepristone and ormeloxifene respectively p=0.924). Baseline RI and PI in mifepristone were 0.71±0.01 and 1.62±0.25 compared to 0.71±0.01 and 1.6±0.23 in ormeloxifene group respectively (p value for RI and PI comparison between groups were 0.909 and 0.736).

Following treatment, in 75%(15) of patients in mifepristone group there was decrease in size of fibroid against only 21%(4) in ormeloxifene group. There was no change in size of fibroid in 5 patients in each group. But none of the patients in mifepristone group showed increase in size. But more than half of patients in ormeloxifene group i.e., 10 (52.63%). P value was found to be significant (<0.001).

Post- treatment ultrasonographic variables of fibroid in both groups did not show significant difference statistically between groups. Mean Volume of fibroid in mifepristone group was lower than in ormeloxifene group following treatment though p value was not significant. (60.83±25.64 vs 71.47±30.34 and p=0.111). Mean PSV and EDV in mifepristone group was 26.36±6.03 and 7.69±1.82 and in ormeloxifene group was 30.57±9.5and 8.83±2.03 with p value 0.105 and 0.073 respectively. S/D ratio was similar in both the groups (3.43±.26 & 3.59±0.31 in mifepristone and ormeloxifene respectively p=0. 0.108). Following treatment, RI and PI in mifepristone were 0.70±0.02 and 1.69±0.22 compared to 0.71±0.02 and 1.677±0.34 in ormeloxifene group respectively (p value for RI and PI comparison between groups were 0.132 and 0.785).

Data was analysed and comparison was made within each group. There was significant difference in fibroid volume, PSV and EDV before and after treatment within mifepristone group. Other ultrasonographic variables did not show significant statisticaldifference within the group when compared before and after treatment. For mifepristone group, change in mean for volume of fibroid was 20.90, p value for pre and post- treatment change being <0.001 whereas for ormeloxifene group, change in mean for volume of fibroid was found to be -3.60. negative value indicating that, there was increase in volume of fibroid paradoxically. Change in mean for PSV and EDV for mifepristone group was 6.09 and 1.57 p value being < 0.001 for both parameters. Change in mean after treatment for S/D ratio, RI and PI was not statistically significant (p >0.05) probably due to small sample size.

De Leo et al used doses ranging from 12.5 to 50 mg daily and reported a reduction in uterine/fibroid volume of 40–50%, with amenorrhoea in most subjects.[8] This report was corroborated 1 year later from a group who used RU 486 at a dose of 5 or 10 mg/day for 1 year, and found that it was effective in decreasing mean uterine volume by 50%, while amenorrhoea occurred in 40–70% of the subjects.

Eisinger et al[9] in 2003 followed up their preliminary findings with the only published RCT to date on the use of mifepristone for the treatment of uterine fibroids. In this study with mifepristone 5mg for 6 months, the mean uterine volume decreased by 48% at 6 months. This was a small study which included 42 women in a double-blind placebo controlled study over a period of 6 months.

Hot flushes were increased over baseline in the 10-mg group, but 5 mg/day did not increase the incidence of vasomotor symptoms. Simple hyperplasia was noted in 28% of the women. This study therefore suggested that a dose of mifepristone as low as 5 mg/day may be efficacious for the treatment of uterine fibroids, with few side-effects.

Fiscella et al 2006[10] reported that overall quality of life was improved significantly, anaemia rates and uterine volume were reduced significantly, and women were more likely to become amenorrhoeic if they were treated with a low dose of mifepristone. Murphy et al[11] found that women with Mifepristone 25mg/day experienced average reduction of 56% at 3 months.

In our study, within ormiloxifene group, change in mean after treatment for PSV, EDV, S/D ratio, RI and PI were all in the negative range indicating increase in volume of fibroid after treatment with ormeloxifene. But p value was < 0.005 for all above mentioned parameters.

In a study on 26 subjects of dysmenorrhea, 57 % showed symptomatic relief. 9 showed no relief, and pain was aggravated in 2 cases following ormeloxifene therapy.[12] In an independent study[13] on 70 patients of DUB receiving 30 mg biweekly dose of ormeloxifene for 6 months, 80% were relieved of menorrhagia at the end of treatment.

Biswas et al. (2004)[14] put forward that ormeloxifene is safe and effective drug in the treatment of dysfunctional menorrhagia. In a pilot study by Datta Ray C (2002) it was seen that there was decrease in bleeding often resulting in amenorrhea with a significant increase in hemoglobin concentration and decrease in uterine size. So, ormeloxifene has been used as a need

oriented contraceptive and is being given for treating dysfunctional bleeding of the uterus.[15]

Conclusion

Results showed that following treatment, in 15(75%) patients in mifepristone group there was decrease in size of fibroid against only 4 (21%) in ormeloxifene group. There was no change in size of fibroid in 5 patients in each group. But none of the patients in mifepristone group showed increase in size whereas, more than half of patients in ormeloxifene group i.e., 10 (52.63%). P value was found to be significant (<0.001). Post-treatment ultrasonographic variables changed accordingly. Change in volume of fibroid and PSV, EDV, S/D ratio, PI and RI were assessed after treatment with study medications.

Volume of fibrod decreased in ormeloxifene group in 4 patients, out of which 3 patients had submucosal fibroid. Volume increased in 10 patients which was paradoxical to the expected result.

The study concludes that, mifepristone can successfully reduce volume of uterine fibroid whereas, the effect of ormeloxifene on uterine fibroid are variable and may cause increase in size of uterine fibroid as in our study (>50%).

Anyhow, studies for assessment of improvement of symptomatology and changes in size of mass conducted on larger sample size with longer follow up are required.

Table 1: Comparison of post-treatment alteration in Volume of fibroid between groups

Alteration volume	Mifepristone	Ormeloxifene	p-value
Decreased	15(75%)	4(21.05%)	<0.001
Nochange	5(25%)	5(26.31)	
Increased	0	10(52.63%)	

Figure 1: Comparison of post- treatment alteration in Volume of fibroid between groups

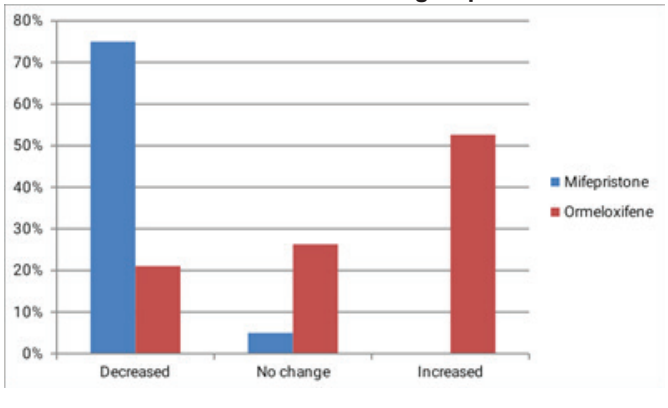

Table 2: Fibroid characteristics in mifepristone group pre and post- treatment

Parameter	Changein mean	Pre-treatment	Post-treatment	p-value
Fibroidvolume (cc)	20.9085	81.7±27.5	60.83±25.64	<0.001
PSV	6.0975	32.46±7.4	26.36±6.03	<0.001
EDV	1.57400	9.26±1.95	7.69±1.82	<0.001
S/DRatio	.05900	3.5±0.23	3.43±.26	0.456
RI	.00500	0.71±0.01	0.70±0.02	0.440
PI	-.07050	1.62±0.25	1.69±0.22	0.299
< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Figure 2: Fibroid characteristics in mifepristone group pre and post- treatment

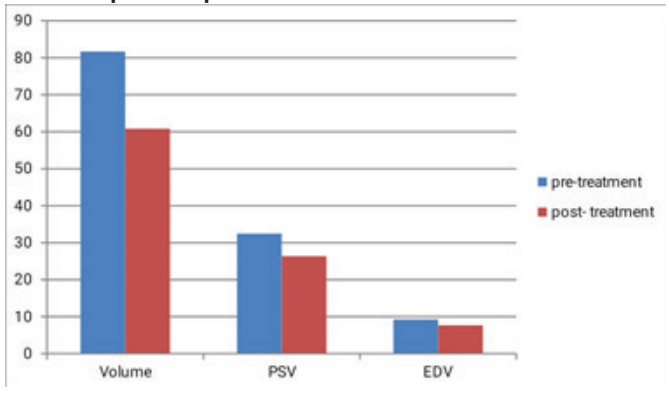

Table 3: Changes in numerical variables within Group A Mifepristone and Group B Ormeloxifene– Paired t test

		Mean	Std. Deviation	Std.Error Mean	95% Clof diffLL	95% Clof diff UL	t	Df	Pvalue
Mifepristone	Pair 1 FibVol1-FibVol2	20.9085	17.0334	3.8088	12.9366	28.8804	5.490	19	<0.001
	Pair 2 PSV1-PSV2	6.0975	5.4683	1.2227	3.5383	8.6567	4.987	19	<0.001
	Pair 3 EDV1-EDV2	1.57400	1.76616	.39492	.74741	2.40059	3.986	19	<0.001
	Pair 4 SDR1 -SDR2	.05900	.34671	.07753	-.10327	.22127	.761	19	.456
	Pair 5 RI1-RI2	.00500	.02838	.00635	-.00828	.01828	.788	19	.440
	Pair 6 PI1-PI2	-.07050	.29539	.06605	-.20875	.06775	-1.067	19	.299
Ormeloxifene	Pair 1 FibVol1-FibVol2	-3.6042	13.8450	3.1763	-10.2773	3.0689	-1.135	18	.271
	Pair 2 PSV1-PSV2	-.8289	7.1984	1.6514	-4.2985	2.6406	-.502	18	.622
	Pair 3 EDV1-EDV2	-.28947	1.14304	.26223	-.84040	.26146	-1.104	18	.284
	Pair 4 SDR1 -SDR2	-.09895	.28657	.06574	-.23707	.03917	-1.505	18	.150
	Pair 5 RI1-RI2	-.00474	.01982	.00455	-.01429	.00482	-1.042	18	.311
	Pair 6 PI1-PI2	-.07158	.40741	.09347	-.26794	.12479	-.766	18	.454

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