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Comparison of Mifepristone and Ulipristal acetate in the treatment of symptomatic uterine fibroids

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Abstract
Aim: To evaluate role of Mifepristone and Ulipristal acetate in the treatment of symptomatic uterine fibroids.
Methods: The present randomized comparative prospective study was conducted among non-pregnant and non-lactating females of age 25-50 years with symptomatic fibroids reported in the Department of Obstetrics & Gynaecology.The selected subjects were divided into two treatment arms i.e. GROUP 1): Ulipristal Acetate: 5mg OD for 3 months and GROUP 2): Mifepristone: 25mg OD for 3 months. A Blood examination, USG (pelvis), PAP, Smear and Endometrial Biopsy was done. Subjects visited the hospital at visit 1, visit 2, visit 3, visit 4, visit 5 and visit 6 for 6 months.
Results: When mean PBAC score at first, second, third, fourth and fifth visit was compared statistically among Ulipristal acetate and Mifepristone group, it was found to be statistically significant. Size was reduced more in Mifepristone group as compared to Ulipristal acetate group at all the different intervals.
Conclusions: We concluded from this study that Mifepristone should be preferred over Ulipristal acetate for treatment of symptomatic fibroids.

Keywords: Ulipristal acetate, Mifepristone, Fibroid uterus, Heavy menstrual bleeding

Introduction
Uterine fibroids (65%) are attributed to inadequate endometrial receptivity to embryo implantation secondary to deleterious effects of uterine fibroids on endometrium. Many women, if given the option, would prefer medical treatment for their Uterine Fibroids over a surgical solution to avoid the possible risks associated with surgery, and preserve their uterus for future fertility and also for psychological/feminine reasons [1].
Surgical interventions include hysterectomy and myomectomy [2, 3]. Various medical therapies used for fibroids include tranexamic acid, combined oral contraceptive pills, GnRH analogs, selective estrogen and progesterone receptor modulators, Somatostatin analogs and aromatase inhibitors [4].
The most commonly used progesterone receptor modulator is Mifepristone (RU486). It binds strongly to endometrial progesterone receptors, minimally to oestrogen receptors and up regulates androgen receptors. It has been shown to decrease myoma size as well as symptoms [5].
Use of Mifepristone and Ulipristal acetate individually has been studied by some researchers but comparative studies of these 2 drugs have rarely been done. For this reason, we have conducted this study to compare efficacy and safety of Mifepristone and Ulipristal acetate in the treatment of symptomatic uterine fibroids.

Material and Methods
The present randomized comparative prospective study was conducted among 120 non-pregnant and non-lactating females of age 25-50 years with symptomatic fibroids reported in the Department of Obstetrics & Gynaecology, Chhatrapati Shivaji Subharti Hospital, Meerut (U.P.) for a duration of 2 years from September 2017 to July 2019. The study protocol for all procedures was approved by the Institutional Review Board for Ethical Clearance and was performed in accordance with the Code of Ethics of the World Medical Association according to the Declaration of Helsinki of 1975, as revised in 2000. All patients were asked to sign a written consent form prior to inclusion in the study. The selected subjects were divided into two treatment arms i.e. GROUP 1): Ulipristal Acetate: 5mg OD for 3 months and GROUP 2): Mifepristone: 25mg OD for 3 months. As per FIGO classification of fibroids, they are classified into various classes like intramural, submucosal, intramural type and further helps in its mode of treatment and the treatment's efficacy. The subjects were selected according to the following inclusion and exclusion criteria:

Inclusion Criteria
Women between 25-50 years, body mass index (BMI) of 18-35 kg/m^2, subjects with symptomatic fibroid, uterine size equivalent to that of a pregnancy of no more than 16 weeks of gestation, uterine fibroid not more than 10cm in diameter and no significant findings on clinical breast examination.

Exclusion Criteria
Pregnant and lactating women, women desirous of pregnancy, genital bleeding of unknown etiology, uterine, cervical, ovarian or breast cancer, hemoglobinopathy (sickle cell anemia, thalassemia), coagulation disorders, Hb $\leq$ 6gm/dl and history of endometrial ablation or uterine artery embolisation for myoma.
Detailed history of the patient, general physical examination and systemic examination like central nervous system, respiratory system, cardio-vascular system was done followed by per abdomen examination, per speculum and per vaginal examination. In per vaginal examination, the position, size, shape, mobility and consistency of uterus along with bilateral adnexa were noted. Detailed menstrual and obstetric history was recorded. At each visit, examination of the patient was done. PBAC Score and

Universal Pain Assessment Score was explained to all participants to be recorded during study period. Complete haematological with biochemical screening was done including haemoglobin, haematocrit, total leucocyte count, differential leucocyte count and ESR. PAP smear and Endometrial sampling was done at the time of recruitment.

Study Visits

Subjects visited the hospital at visit 0 (for evaluation and tests to screen the patients for study), visit 1 (after one week for recruitment and for initiation of treatment), visit 2 (after 1 month for assessment of PBAC score and improvement in symptoms, if any), visit 3 (after 2 months for assessment of PBAC score and improvement in symptoms if any), visit 4 (after 3 months for evaluation of patient), visit 5 (after 4 months for follow up) and visit 6 (after 6 months for follow up).

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). The level of significance was set at $p < 0.05$.

Results

In both the groups, maximum subjects were in the age group of 36-40 years, followed by 41-50 years. The mean age of the study subjects was 37.58±6.41 in Ulipristal group and 36.65±6.22 in Mifepristone group respectively.

PBAC improvement was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group with statistically significant difference as $p<0.05$ (table 1).

Size was reduced more in Mifepristone group as compared to Ulipristal acetate group at all the different intervals, though it was statistically insignificant as $p>0.05$ (table 2).

Increase in ET was found in both the study groups at different intervals. When mean ET at fifth visit was compared statistically among Ulipristal acetate and Mifepristone group, it was found to be statistically significant as $p<0.05$ (table 3). 100% of the subjects were satisfied with the treatment in both the groups.

Table 1: Comparison of PBAC score at different visit among the study groups

PBAC score	Ulipristal acetate		% improvement	Mifepristone		% improvement	t test	p value
	Mean	SD		Mean	SD			
Before	202.65	25.28		204.61	23.41		1.20	0.19
First	174.38	19.37	13.95	161.19	23.41	21.22	7.81	<0.01*
Second	154.18	20.83	23.91	131.39	18.49	35.78	10.92	<0.01*
Third	137.62	22.71	32.09	119.14	19.55	41.77	6.75	0.02*
Fourth	126.48	18.43	37.59	108.89	17.31	46.78	13.14	<0.01*
Fifth	112.89	16.30	44.29	101.71	17.89	50.29	10.64	<0.01*

*: statistically significant

Table 2: Comparison of size (volume) of fibroid among the study groups at different visits

Size	Ulipristal acetate		% improvement	Mifepristone		% improvement	t test	p value
	Mean	SD		Mean	SD			
Before	3.86	1.69		4.11	1.68		1.16	0.22
First	3.52	1.34	24.34	3.37	1.28	32.22	0.27	0.58
Second	3.04	1.27	42.13	2.81	1.07	53.33	0.40	0.57
Third	2.79	1.35	27.72	2.48	1.52	39.66	0.97	0.28
Fourth	2.47	1.40	36.01	2.19	1.30	46.72	1.03	0.24
Fifth	2.30	1.57	40.41	2.04	1.37	50.36	1.29	0.10

Table 3: Comparison of Endometrial Thickness (ET) among the study groups at different visits

ET	Ulipristal acetate		% increment	Mifepristone		% increment	t test	p value
	Mean	SD		Mean	SD			
Before	13.85	0.29		13.06	1.29		0.81	0.62
First	15.32	1.09	10.61	14.40	1.18	10.26	0.59	0.48
Second	16.76	1.01	21.01	15.71	1.37	20.29	0.98	0.34
Third	17.23	1.32	24.40	16.09	1.78	23.20	1.22	0.09
Fourth	17.59	1.41	27.00	16.78	1.91	28.48	0.91	0.29
Fifth	18.41	1.69	32.92	17.32	1.70	32.62	1.54	0.04*

*: statistically significant

Discussion

Progesterone is one of the key players in the female reproductive function. Selective Progesterone receptor modulators (SPRMs) like Mifepristone and Ulipristal Acetate have been used for the treatment of dysfunctional uterine bleeding and uterine myomas because of their anti-proliferative effects on endometrium and myometrium [6].

Mean PBAC score was 202.65 and 204.61 in Ulipristal acetate and Mifepristone group respectively before the intervention and after intervention at fifth visit, the score was 112.89 and 101.71 in Ulipristal acetate and Mifepristone group respectively. PBAC improvement was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group. A study conducted by Col D. Arora *et al* [7]. it was seen that with Mifepristone all patients without exception had amenorrhoea bringing the PBAC score to 'zero'. In one more study conducted by Shradha *et al* [8]. patients out of 50

became amenorrhic, and there is no patient with menorrhagia at the end of treatment. Therefore, Mifepristone is a reasonable choice of treatment in perimenopausal age group and patients who want to avoid surgery.

In the present study ET improvement was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group. Similar results were reported by Shikha Seth *et al* [9]. who revealed that endometrial thickness (ET) at start of treatment was 7.6±2.8 which progressively increased in all '82' cases during the treatment phase with mean 51.9% rise over three months.

In the present study, mean fibroid size reduction was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group. Ashish R. Kale [10]. revealed that Mifepristone was associated in reduction in size of fibroids by 55% and 40% in patients having fibroid size of more than 3-5 cm and less than 3 cm respectively. Feng C [11]. in their comparative study of women with symptomatic uterine fibroids who were treated with 5 mg or 2.5 mg of Mifepristone or placebo found that treatment with Mifepristone was associated with significant improvement in health-related quality of life.

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Conflict of interest
None declared

Ethical approval
Not required

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