Original Research Article

Role of selective progesterone receptor modulators in the treatment of symptomatic uterine fibroids

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ABSTRACT

Background: Uterine leiomyomas are benign tumours of smooth muscle cells and fibrous tissue that develop within the wall of the uterus. Objective of this study was to compare efficacy and safety of Mifepristone and Ulipristal acetate in the treatment of symptomatic uterine fibroids.

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 and gynecology, Chhatrapati Shivaji Subharti Hospital, Meerut, Uttar Pradesh for a duration of 2 years from September 2017 to July 2019.The selected subjects were divided into two treatment arms i.e. Group 1: ulipristal acetate: 5 mg OD for 3 months and Group 2: mifepristone: 25 mg OD for 3 months. Detailed history of the patient, general physical examination and systemic examination was done followed by per abdomen examination, per speculum and per vaginal examination. 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: In both the groups, maximum subjects were in the age group of 36-40 years, followed by 41-50 years. 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. Uterine pain was reduced more in mifepristone group as compared to ulipristal acetate group at all the different intervals. Size was reduced more in mifepristone group as compared to ulipristal acetate group at all the different intervals.

Conclusions: Authors conclude from this study that mifepristone should be preferred over ulipristal acetate for treatment of symptomatic fibroids.

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

INTRODUCTION

Uterine leiomyomas are benign tumours of smooth muscle cells and fibrous tissue that develop within the wall of the uterus.[1] They may grow as a single tumor or in clusters and one such single fibroid can measure up to 20 cm or more and may range in size from seedlings to large uterine tumors.[2] Uterine fibroids (UFs) are the most frequent tumor of the female genital tract with an increasing frequency during the women's fertile years with a prevalence of 20-77% depending on the population and method of assessment.[3-5] Its incidence increases with increasing age and the life time risk for women to develop uterine fibroids is 70%.[6] Uterine fibroids (65%) are attributed to inadequate endometrial receptivity to embryo implantation secondary to deleterious effects of uterine fibroids on endometrium.[7] 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.[8]

Surgical interventions include hysterectomy and myomectomy.[9,10] Other less invasive procedure include uterine artery embolization and magnetic resonance guided focused ultrasound surgery (MRgFUS).[11] Various medical therapies used for fibroids include tranexamic acid, combined oral contraceptive pills, GnRH analogues, selective estrogen and progesterone receptor modulators, somatostatin analogues and aromatase inhibitors.[12]

Owing to their pharmacological properties, SPRMs have been tested or are under development in the indication of uterine fibroids. Ulipristal acetate is the only molecule which has received marketing authorization for a pre-surgical 3-month treatment of uterine fibroids. Three other SPRM have been tested for the indication of uterine fibroids: mifepristone, asoprisnil and telapristone acetate.[13] 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.[14] 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, authors have conducted this study to compare efficacy and safety of mifepristone and ulipristal acetate in the treatment of symptomatic uterine fibroids.

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 and gynecology, Chhatrapati Shivaji Subharti Hospital, Meerut, Uttar Pradesh 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 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 ≤6 gm/dl, history of endometrial ablation or uterine artery embolization for myoma, women with history of current treatment for myoma with any drug like GnRH Agonist, women with history of hormonal intake in last 2 months, women with history of hormonal contraception intake in last 2 months, known case of hepatic or renal impairment, neurological disease, endocrinal disease or severe asthma and women with heavy menstrual bleeding in preceding cycle.

Study groups

The selected subjects were divided into two treatment arms i.e. Group 1: ulipristal acetate: 5 mg OD for 3 months and Group 2: mifepristone: 25 mg 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.

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 hematological with biochemical screening was done including haemoglobin, hematocrit, total leucocyte count, differential leucocyte count and ESR. Pap smear and endometrial sampling was done at the time of recruitment.

Examination

At 1st visit, general, systemic and pelvic examinations were done, pregnancy was excluded and sample was taken for investigations. Clinical examination i.e. per speculum and per vaginum was done in every visit. The reports were reviewed before recruitment of the patients. Baseline ECG and USG (Abd/TVS) of every patient was done. USG was done in every visit and changes were noted in size of fibroid and uterus, volume of fibroid, ET of uterus, vascularity etc.

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). Difference between two groups was determined using student t-test as well as Chi-square test and the level of significance was set at p<0.05.

RESULTS

A total of 64 and 66 patients gave consent for ulipristal and mifepristone treatment respectively. No. of subjects drop outs in subsequent visits were 4 and 6 in for Ulipristal and Mifepristone group respectively. Finally, 60 patients were left in both the groups as shown in Figure 1. 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 (Figure 2). In this study, 41.7% of the subjects in ulipristal acetate as well as mifepristone group were post-graduates. Graduation was done by 35% in ulipristal and 51.7% in mifepristone group.

PBAC improvement was found in both the study groups at different intervals, but it was comparatively more in mifepristone group. However, few patients in both the groups have experienced amenorrhoea. 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 as p<0.05 (Table 1).
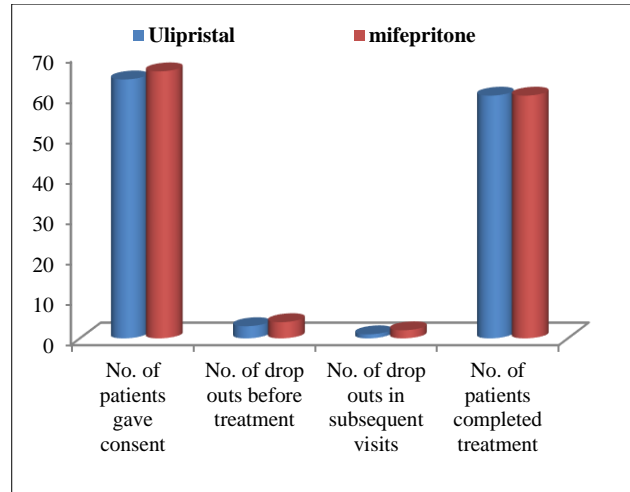

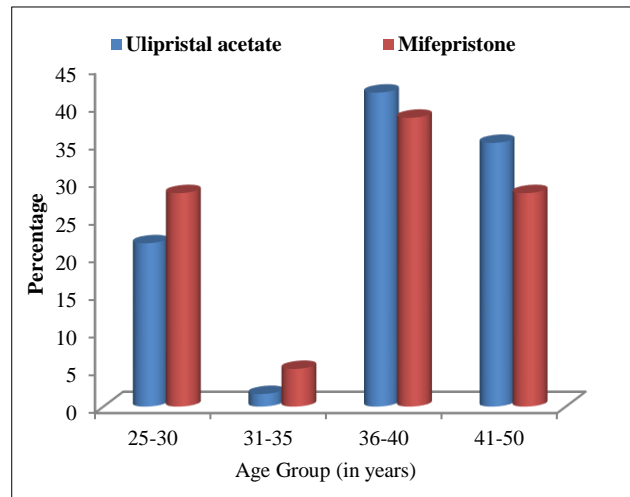**Figure 1: Follow-up of patients.**

Figure 2: Age distribution of the study 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.

Uterine pain was reduced more in mifepristone group as compared to ulipristal acetate group at all the different intervals. When mean uterine pain assessment at first, second, third, fourth and fifth visit was compared statistically among ulipristal acetate and mifepristone group, it was found to be statistically significant as p<0.05 (Table 2).

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 3). 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 4).

Figure 3 shows that 100% of the subjects were satisfied with the treatment in both the groups.

Table 2: Comparison of uterine pain assessment at different visit among the study groups.

Uterine pain assessment	Ulipristal acetate		% improvement	Mifepristone		% improvement	t-test	p-value
	Mean	SD		Mean	SD			
Before	8.83	2.81		8.72	2.29		0.42	0.59
First	6.68	2.47	24.34%	5.91	1.92	32.22%	1.57	0.04*
Second	5.11	2.16	42.13%	4.07	1.98	53.33%	2.79	0.02*
Third	4.28	1.91	51.53%	3.43	1.67	60.67%	2.60	0.03*
Fourth	3.73	1.98	57.76%	2.90	1.79	66.74%	1.34	0.11
Fifth	3.14	2.14	64.44%	2.57	1.92	70.53%	2.48	0.04*

Table 3: 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 4: Comparison of endometrial thickness (ET) among the study groups at different visits.

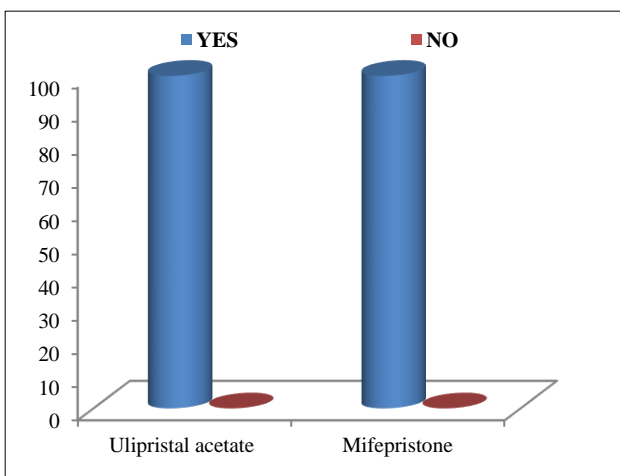| ET	Ulipristal acetate		% Increment	Mifepristone		% Increment	t-test	p-value
	Mean	SD		Mean	SD			
Before	13.85	0.29		13.06	1.29		0.81	0.62
First	15.32	1.09	10.61%	14.40	1.18	10.26%	0.59	0.48
Second	16.76	1.01	21.01%	15.71	1.37	20.29%	0.98	0.34
Third	17.23	1.32	24.40%	16.09	1.78	23.20%	1.22	0.09
Fourth	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.

Figure 3: Satisfaction level in both groups.

DISCUSSION

Progesterone is one of the key players in the female reproductive function. In the uterus, progesterone regulates the growth and differentiation of endometrial and myometrial cells, and is therefore a counter player to estrogen. Progesterone may have inhibitory and stimulatory effects on cell proliferation.[15] 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.[16]

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 Arora CD et al, it was seen that with mifepristone all patients without exception had amenorrhea bringing the PBAC score to 'zero'.[17] In one more study conducted by Shradha et al, patients out of 50 became amenorrhea, and there is no patient with menorrhagia at the end of treatment.[18] Therefore, Mifepristone is a reasonable choice of treatment in perimenopausal age group and patients who want to avoid surgery.

In the present study mean pain score was 8.83 and 8.72 in ulipristal acetate and mifepristone group respectively before the intervention and after intervention at fifth visit, the score was 3.14 and 2.57 in ulipristal acetate and mifepristone group respectively. Pain improvement was found in both the study groups at different intervals, but it was comparatively more in mifepristone group. Kale AR in his study found ulipristal acetate and mifepristone, in women with symptomatic fibroids were associated with decreased pain.[19] It was observed that mifepristone was more effective in reducing pain than ulipristal acetate in patients having fibroid size of less than 3 cm.

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 Seth S et al, 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.[20]

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. Kale AR 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.[19] Feng C21 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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