ORIGINAL RESEARCH

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

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Abstract
Aim: To compare efficacy and safety of Mifepristone and Ulipristal acetate in the treatment of symptomatic uterine fibroids.
Material and method: This comparative prospective study was conducted in the Department of Obstetrics & Gynaecology among 120 patients comprised of non-pregnant and non-lactating females of age 25-50 years with symptomatic fibroids coming to the department OPD. 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. 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, ESR etc.
Results: Treatment of symptomatic fibroids by Mifepristone as well as Ulipristal acetate was associated with reduction in fibroid size, reduced blood loss and decreased pain. It was found that overall Mifepristone was found to be more effective compared to Ulipristal acetate.
Conclusion: We conclude from this study that both these drugs can be used for treatment of symptomatic fibroids. Mifepristone should be preferred over Ulipristal acetate for treatment of symptomatic fibroids.
Keywords: Mifepristone, Ulipristal acetate, Symptomatic Uterine Fibroids

Introduction:
Uterine fibroids (UFs) are the most frequent tumorof the female genital tract with an increasingfrequency during the women's fertile years with a prevalence of 20–77% depending on thepopulation and method of assessment[1]. Its incidence increases with increasing age and thelife time risk for women to develop uterine fibroids is 70%[2]. Uterine fibroids are more frequentand appear at an earlier age in black women, whereas the incidence of fibroids inAsian or Hispanic women is comparable to the incidence in Caucasian women[3].Patients can also manifestate with fertility disorders or recurrent miscarriages. However, some patients may also haveno medical complaints[4]. Anterior wall fibroids can cause pressure symptoms on bladder and hence increase frequency of micturition. Posterior wall fibroids lead to spontaneous abortions, infertility etc. The treatment of uterine fibroids depends upon the size, symptoms, location and age of the patient. Patients who are asymptomatic and in whom there are very minimal symptoms these fibroids should be left alone, and no active intervention is required. In patients having severe symptoms affecting quality of life considerable surgical management may be required[6].Surgical interventions include hysterectomy and myomectomy. Less invasive procedures such as uterine artery embolization uses embolus to block blood flow to the tumor, which consequently reduces fibroid size and its associated symptoms. Minimally invasive surgeries like hysteroscopic myomectomy (for submucosal fibroids), Laparoscopic myomectomy (for symptomatic subserosal and less commonly for intramural fibroids), abdominal myomectomy and hysterectomy (when woman no longer wishes to preserve uterus or fertility like in perimenopausal

women or in women where sarcomatous changes are suspected on imaging)[6,7].Other less invasive procedure include uterine artery embolization and magnetic resonance guided focused ultrasound surgery (MRgFUS)[8]. Medical management is used in patients for short term relief and as pre-operative adjunct treatment for reduction of size of the fibroid. Nonetheless many of the studies have come up with the conclusion that medical management may be used for small sized fibroids. 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[9].Owing to their pharmacological properties, SPRMs weremainly tested in indications which are supposed to have a relationto the role of progesterone, mainly in gynaecologicalandoncological indications. Only few SPRMs have been tested or are under development in the indication of uterine fibroids.Ulipristal acetate is the only molecule which has received marketingauthorization for a pre-surgical 3-month treatment ofuterine fibroids. Three other SPRM have been tested for theindication of uterine fibroids: mifepristone, asoprisnilandtelapristone acetate[10].The most commonlyused progesterone receptor modulator is mifepristone (RU486). It binds strongly to endometrial progesteronereceptors, minimally to oestrogen receptors and upregulatesandrogen receptors. It has been shown to decrease myomasize as well as symptoms[11]. Reduction in size withmifepristone might be due to the direct effect in reducingnumber of progesterone receptors. It has been observed that ovarian acyclicity is present with use of mifepristone leading to hormonal levels similar to early follicular phase,which also inhibit steroid dependent growth of myoma.Mifepristone also delays or inhibits ovulation, which mayproduce amenorrhoea. It has got a direct suppressive effect on endometrial vasculature which accounts for reducingmenstrual blood loss[12].

Hence various treatment options of fibroids include observation and follow up (in small asymptomatic fibroids), medical management (Mifepristone or Ulipristal acetate), uterine fibroid embolisation and surgery(hysterectomy/ myomectomy). 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 method: Thiscomparative prospective study was conducted in the Department of Obstetrics & Gynaecology among 120 patients comprised of non-pregnant and non-lactating females of age 25-50 years with symptomatic fibroids coming to the department OPD.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.
- On clinical breast examination no significant findings

Exclusion Criteria

- Pregnant and lactating women
- Women desirous of pregnancy
- Genital bleeding of unknown etiology
- Uterine, cervical, ovarian or breast cancer
- History of endometrial ablation or uterine artery embolisation for myoma
- 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
- 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: 5mg OD for 3 months
- GROUP 2): Mifepristone : 25mg OD for 3 months

Methodology: The women coming to the Gynae OPD of the department of Obstetrics and Gynaecology in the age group of 25-50 years diagnosed with symptomatic uterine fibroids were taken as study material.Patients were blindly randomized to either of the treatment arms.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, ESR etc.The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The

patients who fulfilled exclusion and inclusion criteria were interviewed for the demographic, socioeconomic status, medical history and previous history of taking any medications and supplements and blindly randomized to one of the 2 groups (ulipristal/mifepristone).

Examination: At 1st visit, general, systemic and pelvic examinations were done, pregnancy was excluded and sample was taken for investigations i.e.

a. Hb with haematocrit (done in every visit)
b. TLC
c. DLC
d. ESR
e. Platelet count
f. RBS
g. KFT
h. LFT (done at 0 visit and after third month)
i. Coagulation profile
j. TSH
k. PAP Smear
l. Histopathological examination of endometrium (HPE)
m. USG/ TVS (done in every visit)
n. Clinical examination: per speculum and per vaginum (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.

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: The mean age of the study subjects was 37.58±6.41in 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. 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).

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 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).

Dysmenorrhea reduction was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group. When mean dysmenorrhea reduction at all the visits (except fifth) was compared statistically among Ulipristal acetate and Mifepristone group, it was found to be statistically significant as $p<0.05$ (table 5).

Hct improvement was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group. When mean Hct score at 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 6).

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 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

Table 5: Comparison of dysmenorrhea among the groups at different visits

Dysmenorrhea	Ulipristal acetate		% improvement	Mifepristone		% improvement	Chi square	p value
	n=60	%		n=60	%			
Before	28	46.7		24	40		2.17	0.42
First	21	35	25	14	23.33	41.67	3.53	0.04*
Second	15	25	46.43	6	10	75	3.67	0.04*
Third	11	18.33	60.71	3	5	87.5	3.98	0.03*
Fourth	9	15	67.86	2	3.33	91.67	7.89	0.01*
Fifth	5	8.33	82.14	2	3.33	91.67	2.14	0.23

*: statistically significant

Table 6: Comparison of Hematocrit at different visits among the study groups

Hct	Ulipristal acetate		% improvement	Mifepristone		% improvement	t test	p value
	Mean	SD		Mean	SD			
Before	34.30	3.55		33.61	3.41		1.20	0.19
First	37.42	3.18	9.09	37.91	3.12	12.79	0.91	0.26
Second	37.98	3.04	10.73	38.99	2.92	16.01	1.91	0.03*
Third	38.23	2.98	11.46	39.32	1.98	16.99	2.34	0.03*
Fourth	38.43	3.08	12.04	39.57	2.19	17.73	2.39	0.03*
Fifth	38.76	3.20	13.00	39.89	2.54	18.68	2.58	0.02*

*: statistically significant

Discussion: 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. The authors examined the effects of daily administration of mifepristone 25 mg and Ulipristal acetate 5mgfor a period of 3 months with uterine fibroids.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±6.41in ulipristal group and 36.65±6.22 in Mifepristone group respectively. Rajat Kumar Ray etal[13] in his study revealed maximum number of patients were of 36 to 40 years (16 in number). Cases in age group 41 to 45 were 14 in number followed by 31 to 35 years age group (12in number). Rest 8 cases were of age group 24 to 30 years. This is similar to the present study. Jacques Donnezet al[14] reported mean age of approximately 41 years in his study. Shikha Seth et al[15] also reported similar mean age in their study i.e. 38.47 ± 4.9 years. Ashish R. Kale[16] found mean age of 38.6±5.8years and 39.4±6.1 years in Mifepristone and Ulipristal acetate group respectively. This can be clearly explained by the fact that fibroids are more common in middle age group.In the present study, all the subjects had PBAC score of >100 before the start of treatment in both the study groups. Anita Kant et al[17] reported PBAC>100 among 71.75 of the study subjects. 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 inUlipristal 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. However, few patients in both the groups have experienced amenorrhoea. Kulshrestha et al[18] conducted a study in which PBAC score significantly reduced from 253 to 19.8 in 25 mg daily and from 289 to 104 in 10mg group, after 3 months of treatment. Sabitaet al[19] conducted a study in which the mean blood loss declined in 100% of the patients. A study conducted by Eisengeret al[20] showed a significant difference of 7.1units of menstrual blood loss index in the two groups. In yet another study conducted by Col D. Arora et al[21], it was seen that with Mifepristone all patients without exception had amenorrhoea bringing the PBAC score to 'zero'. Jacques Donnez et al[14] in his study found that PBAC score progressively reduced from medians of >200 at the start of the first course to <100 after the end of the second ulipristal acetate course in both treatment groups (Ulipristal acetate 5 mg and Ulipristal acetate 10 mg).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. Percentage improvement in pain score was 24.34, 42.13, 51.53, 57.76 and 64.44 at first, second, third, fourth and fifth visit respectively in Ulipristal acetate group and the same was found to be 32.22, 53.33, 60.67, 66.74 and 70.53 respectively in Mifepristone group with statistically significant difference in the present study.Ashish R. Kale[16] in his study found Ulipristal acetate and Mifepristone, in women with symptomatic fibroids were associated with decreased pain.While it was found that Mifepristone was more effective in patients having smaller fibroids (less than 3 cm),Ulipristal acetate was more effective in medical management of the patients having fibroids of relatively larger size (3-5 cm). Treatment with Ulipristal acetate was associated with significant pain reduction in patients having fibroid size of 3-5 cm (60%) while in patients having fibroid size less than 3 cm the most profound effect was seen in reduction in menorrhagia (45%). It was observed that Mifepristone was more effective in reducing pain than Ulipristal Acetate in patients having fibroid size of less than 3 cm.Shikha Seth et al[15] conducted a study with 25mg mifepristone for 3 months. Symptom scores for pain showed significant change from average ‘4’ at start of treatment to ‘2’ at end of treatment.Mean ET score was 13.85 and 13.06 in Ulipristal acetate and Mifepristone group respectively before the intervention and after intervention at fifth visit, the score was 18.41 and 17.32 in Ulipristal acetate and Mifepristone group respectively. 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[15] 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. Only in two cases ET crossed the 20 mm mark, after which endometrial biopsy was done and simple endometrial hyperplasia was diagnosed in both the cases.Dysmenorrheabefore the intervention was 46.7% and 40% among the Ulipristal acetate and Mifepristone group respectively. Dysmenorrhea was found among only 8.33% and 3.33% of the subjects in Ulipristal acetate and Mifepristone group respectively in the present study.JacquesDonnez et al[14] in his study found that median visual analogue scale painscores for patients receiving 5 and 10 mg of ulipristal acetatedecreased substantially from baselines of 39.5 and 43.0 respectively to 6.0 (both treatment groups) at the end of course 1. There was some relative return of painwhen menstruation resumed during the off-treatment period(median scores, 22.5 and 22.0) before decreasing again to mediansof 6.0 and 5.0 at the end of the second treatment coursefor patients receiving 5 and 10 mg, respectively.QiShenet al[22] in their study stated that Mifepristone, as a conservative treatment,

effectivelyreduced symptoms, including hypermenorrhea,pelvic pain, pelvic pressure, anemia, and dysmenorrhea.Fibroid size reduction was found in both the study groups at different intervals, but it was comparatively more in Mifepristone group. Percentage reduction in size was 24.34, 42.13, 27.72, 36.01 and 40.41 at first, second, third, fourth and fifth visit respectively in Ulipristal acetate group and the same was found to be 32.22, 53.33, 39.66, 46.72 and 50.36 respectively in Mifepristone group with statistically significant difference in the present study.Ashish R. Kale[16] 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.Ulipristal acetate 10 mg daily was associated with reduction in fibroid size in 80% and <20% in patients having fibroid size of 3-5 cm and less than 3 cm respectively.Shikha Seth et al[15] in their study found that 25 mg Mifepristone reduced uterine size to 63.69%of baseline (−36.4% decline) while Bagaria et al[23], had26.6% reduction with 10 mg over 3 months.EnglundKet al[24]found that fibroid volume (mean±SE) decreased 21.9±4.8% after 4 weeks, 39.5±6.6% (P <0.001) after 8 weeks, and 49.0±9.2% (P <0.001) after 12 weeks of treatment compared to pre-treatment measurements. They further found that administration of mifepristone was associated with a significantly reduced immunoreactivity in fibroids as compared with tissues from untreated patients, this suggested that mifepristone caused regression of fibroids by through a direct antiprogesterone effect.

Conclusion: Treatment of symptomatic fibroids by Mifepristone as well as Ulipristal acetate was associated with reduction in fibroid size, reduced blood loss and decreased pain. It was found that overall Mifepristone was found to be more effective compared to Ulipristal acetate. We conclude from this study that both these drugs can be used for treatment of symptomatic fibroids. Mifepristone should be preferred over Ulipristal acetate for treatment of symptomatic fibroids.

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