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Efficacy and Safety of Mifepristone vs Ulipristal Acetate in Medical Management of Fibroid- A Comparative Study

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Abstract
Background: *Uterine fibroids are a non-cancerous benign tumor that originates from the smooth muscle layer and the accompanying connective tissue of uterus. A majority of women suffering from fibroids remain largely asymptomatic. Medical management of fibroids aims at providing an alternative to those patients who earlier had only surgical options.*
Mifepristone and Ulipristal Acetate are Selective Progesterone Receptor Modulator that reduce the size of the fibroid and uterine volume and hence have the potential to provide relief from symptoms.
Aim: *This study was performed to compare the efficacy and safety of Mifepristone vs. Ulipristal acetate for the treatment of symptomatic uterine fibroids.*
Method: *This study was conducted in the outpatient department of obstetrics and Gynecology, S. N. medical college, Agra. 100 female patients fulfilling the inclusion and exclusion criteria were selected for the study.*
Conclusion: *We conclude from the study that both the drugs can be used effectively for the treatment of uterine fibroids but Mifepristone proved to be better in reducing fibroid size.*
Keyword: *Fibroid, Mifepristone, Ulipristal Acetate.*

Introduction

An uterine fibroid is the most common type of benign tumor of uterus and also the most common pelvic tumor in women. It occurs one in every four or five women of reproductive age, typically reported in 20-40%of reproductive age group women.

To date therapeutic options for long term treatment of uterine fibroids have been very limited with surgery being the main treatment for more than 100 years due to large recurrences of tumors.

Selective progesterone receptor modulators (SPRMs) are a new class of drugs having mixed agonist-antagonist activities which acts by attaching to the progesterone receptor.

Ulipristal acetate is used for medical management of Uterine Fibroids and as an emergency contraception. Its use as an emergency contraceptive has been found safe and without unexpected or serious adverse events. A study demonstrated that UPA can significantly delay follicular rupture when given immediately before ovulation.UPA, acting as a progesterone receptor antagonist, inhibits the proliferation of myoma cells and induces apoptosis by increasing cleaved caspase-3 expression and decreasing Bcl-2 expression.[1-2] It also down regulates the

expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and their receptors. This results in a suppression of neo-vascularization, cell proliferation and cell survival in myoma cells, but not in the surrounding healthy myometrial cells.[3]

Mifepristone acts by binding strongly to endometrial progesterone receptors, minimally to estrogen receptors and upregulates androgen receptors[4]. Reduction in size of fibroids with mifepristone is also believed to be due to the direct effect in reducing number of progesterone receptors. Besides, because of ovarian acyclicity seen with mifepristone, hormonal milieu similar to early follicular phase may also inhibit steroid dependent growth of myoma. Increase in androgen receptors also contributes to anti-proliferative effects[5].

Mifepristone also delays or inhibits ovulation, which may produce amenorrhoea.

Materials and Methods

The present prospective comparative study was conducted in the outpatient department of Obstetrics and Gynaecology, S.N. Medical College, Agra.

Selection of Cases:

Hundred cases presenting with symptoms suggestive of fibroid (menorrhagia, dysmenorrhea, pain in abdomen, pressure symptoms) with ultrasonographically diagnosed fibroid of size more than 2 cm were selected from our outpatient department. The patients were divided into two groups of 50.

Group I (Ulipristal acetate group): They were given Ulipristal acetate in dose 5mg once daily starting from day 4 of menstrual cycle for 3 months.

Group II (Mifepristone group)-They were given Mifepristone 10 mg once daily starting from day 4 of menstrual cycle for 3 months.

Inclusion Criteria

1) Symptomatic women of age group 18 - 45 years of age.
2) Presently not willing for fertility during the course of treatment
3) Size of the fibroid $\geq$ 2 cm
4) All types of leiomyoma single /multiple (intramural / subserosal / submucosal) were be included.
5) Unfit / not willing for surgery
6) Willing to give informed consent
7) Ready to use non-hormonal contraception throughout the study.

Exclusion Criteria

1) Pregnant Women
2) Presently willing for pregnancy during the course of treatment
3) Postnatal upto 6 months
4) Lactating women
5) Having hepatic/renal dysfunction
6) Patients with unexplained bleeding
7) Patients not giving consent for study

Informed consent was obtained from all the patients. Detailed history including, presenting complaints, and detailed menstrual cycle history along with PBAC (Pictorial Blood Loss Assessment Chart)score was also taken. All the cases were subjected to biochemical investigations. The amount of menstrual blood flow was assessed by PBAC score and a score of >100 was taken as menorrhagia.

A total of 4 visits were scheduled.

First visit (1 month after initiation of therapy):

- Detailed history of menstrual cycle and symptomatic relief in complains assessed by 5 point Likert Scale.[6]
- Changes in PBAC score[7]
- Biochemical investigations
- Side effects – amenorrhea, nausea, vomiting, hot flushes, headache, fatigue

Second visit (2 months after initiation of therapy):

- Liver function test

Third visit (3 months after initiation of therapy): Same investigations as first visit. Additional investigations were,

- Transvaginal ultrasound

- Endometrial aspirate to categorize the endometrium [PAEC (progesterone receptor modulator associated endometrial changes), Proliferative endometrium, Secretory endometrium, Asynchronous, Hyperplasia without atypia]

Fourth visit (3 months post treatment follow-up):

- Same investigations as third visit.

At the end of the treatment the analysis was done on the basis of:

Primary Outcome:

- Changes in size of fibroid
- Changes in PBAC score

Secondary Outcome:

- Increase in Haemoglobin levels
- Symptomatic relief in patients
- Safety of the drug by evaluating the side effects

Results

Table No. 1: Distribution according to presenting symptoms

Symptoms	Group I (Ulipristal Acetate group)		Group II (Mifepristone group)	
	No	%	No	%
Menorrhagia	43	86	41	82
Dysmenorrhoea	20	40	22	44
Dyspareunia	5	10	6	12
Pelvic Pain / Pelvic Mass	18	36	21	42
Back Pain	10	20	10	18

Mean age in Group I was 38.3 years and in Group II was 39.1 years. Maximum no. of cases in our study were Para 2 and married. Most common presenting complain in both the groups was menorrhagia wih 86% cases in group I and 82% cases in Group II and dysmenorrhea with 40% cases in Group I and 4% cases in Group II.

Table No. 2: Comparision of mean myoma volume reduction in two groups

Duration	Group I (Ulipristal Acetate group)		Group II (Mifepristone group)	
	Mean	SD	Mean	SD
0 Month	35.41	14.64	34.85	13.91
3 Months	27.85	13.80	23.95	12.41
P value	0.0055		<0.0001	
% reduction	21.34%		31.2%	

On comparing the mean myoma volume reductionit was found that both the drugs were significantly able to reduce myoma volume with Ulipristal acetate showing 21% reduction and Mifepristone showing 31% reduction at the end of the therapy

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Table 3: Mean reduction in PBAC (Pictorial Blood Loss Assessment Chart) score

	Group I (Ulipristal Acetate group)		Group II (Mifepristone group)	
	N	Mean PBAC score	N	Mean PBAC score
Pretherapy	50	262.8	50	257.28
1 month	50	54.42	50	50.88
3 month	49	24.98	50	18.08
6 month	40	100.96	42	99.4

On assessing the change in PBAC score, we found that the PBAC score reduced significantly, i.e., in Group I from 262.8 (pretherapy) to 24.98 (3 months treatment), in Group II from 257.28 (pretherapy) to 18.08 (3 months treatment).

Table 4: Mean rise in Haemoglobin levels(in gms)

Hb levels (gms)	Group I (Ulipristal Acetate group)		Group II (Mifepristone group)	
	N	Mean Hb (in gms)	N	Mean Hb (in gms)
Pretherapy	50	9.346	50	9.508
1 month	50	9.568	50	9.722
3 month	49	10.186	50	10.164
6 month	40	10.836	42	10.514

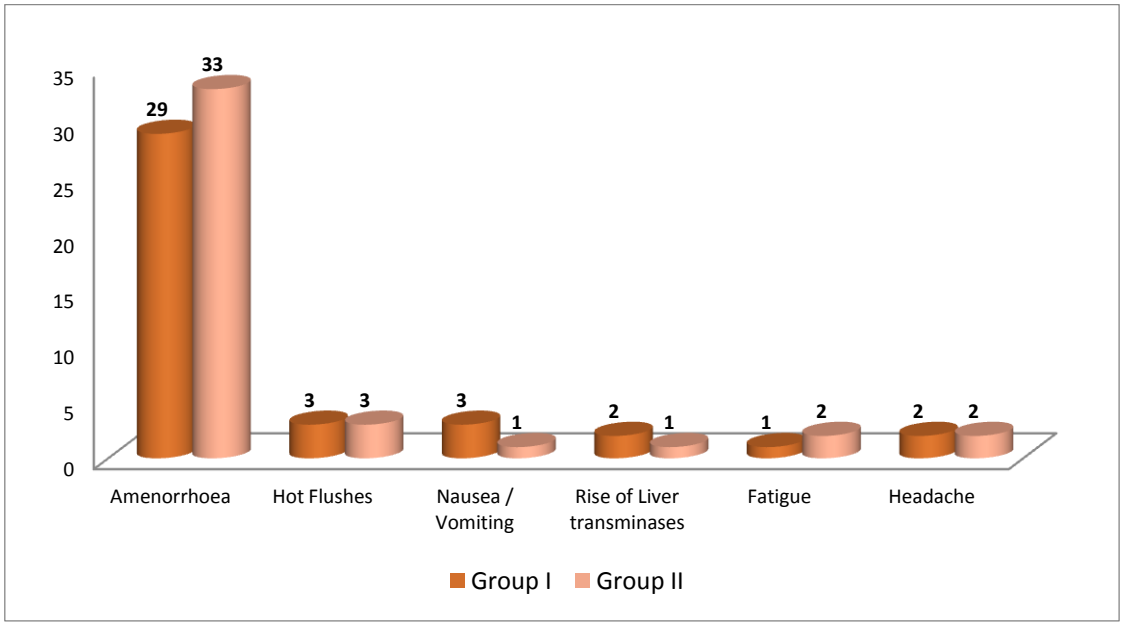
Both the drugs were able to increase the mean levels of haemoglobin from 9.346 in Group I and 9.508 in Group II before the therapy to 10.186 &10.164 respectively after 3 months of therapy, but the rise in levels was insignificant.

Table No. 5 : Changes in endometrial histology

HPE	Group I						Group II					
	0 month		3 month		6 month		0 month		3 month		6 month	
	No	%	No	%	No	%	No	%	No	%	No	%
PAEC	0	0	22	45	14	40.35	0	0	17	34	11	26.1
Secretory Endometrium	20	40	03	6	7	17.5	18	36	5	10	9	21.4
Proliferative Endometrium	14	28	18	37	09	22.5	12	24	20	40	12	28.5
Asynchronous	11	22	01	2	8	20	14	28	5	10	7	16.6
Hyperplasia without atypia	05	10	05	10	02	5	06	12	03	6	3	7.1
TOTAL(n)	**n=50**	**100**	**n=49**	**100**	**n=40**	**100**	**n=50**	**100**	**n=50**	**100**	**n=42**	**100**

There were no malignant changes seen in endometrial histopathology and it can be concluded that the proliferative changes were found to be reversible after the cessation of the treatment.

Bar graph: Assessment of side effects



The above bar graph shows the various side effects experienced by the cases during the course of treatment. Amenorrhoea being the major side effect was seen in 72% of cases in Ulipristal acetate group (Group I) and 78.5% of cases in Mifepristone group (Group II).Menstruation resumed in all cases after median 35 days (range 30 - 42 days).

Discussion

In this study, the presenting complaints of most of the cases was menorrhagia which was about 86% in Group I and 82% in Group II. Prasad *et al.*[8], 2019 in his study found menorrhagia 60% and dysmenorrhoea 40% at the start of the treatment.

We also compared the mean reduction in fibroid volume at the end of the treatment. Mean value of the volume of fibroma was taken in both the groups in terms of (cm^3). The mean fibroid volume at the start of the treatment in Group I & II were 35.41 and 34.85 respectively and at the end of 3 months were 27.85 and 23.95 respectively. Thus the mean reduction in myoma volume was found to be significant. Although, Mifepristone was able to significantly reduce the fibroid volume to 31.2% as compared to 21.34% reduction seen by Ulipristal acetate. Even though the size of the myoma had increased after 3 months post treatment follow up ie 31.24 in Group I and 27.59 in Group II but not to the initial value.

The mean PBAC score of both the groups at the start show that severe menorrhagia was likely in most of the patients. After the three month of treatment the mean PBAC in both groups reduced drastically to 25 in Group I and 18 in Group II. After 6 months though the score was increased i.e. 100 in Group I and 99 in Group II but the increase was not to the initial value.

We also compared the effect of both drugs on haemoglobin levels. The baseline mean levels at the start and at the end of 3 months in Group I were 9.346 and 10.836 and in Group II were 9.508 and 10.164.This difference was found to be statistically not significant.

The pretherapy endometrial histology in our study showed that the maximum cases in both the groups had proliferative and secretory endometrium with a few having hyperplasia without atypia.On comparing the histology after 3 months of therapy maximum cases in Group I had PAEC (progesterone receptor modulator associated endometrial changes) and in Group II had proliferative endometrium. There were no cases with hyperplasia with atypia or any malignant changes. Jayashree et al.[10], 2020 in a prospective study for medical management of myoma found that after 3 months of treatment with Mifepristone 25mg the endometrial pattern was predominantly proliferative (94%) and secretory (6%).There was no abnormal pattern like endometrial hyperplasia or atypia or any other malignant change in the endometrium after the treatment. Donnez et al.[10],2014 in a double blind 12 week course with Ulipristal Acetate 5-10mg showed that approximately 60 % of patients showed PAEC and was fully reversible 6 months after the treatment.

On assessing both the groups on safety profile no serious side effects were seen with Mifepristone group but in Ulipristal group there was rise of liver transaminase level to twice the normal value after 2 months of therapy which led to the discontinuation of the drug. About 75% of cases in both the groups develop amenorrhoea by the end of treatment thereby reducing the amount of flow and improving the quality of life. Menstruation resumed after a period of median 35 days (range 30-42 days). Ekanem *et al.*[11], 2020 in his study summarized the liver safety profile from PEARL studies. PEARL I revealed three patients who had liver enzyme levels (ALT)>3 times the higher end of normal. PEARL II & III, no patient had ALT levels exceeding the higher end of normal In PEARL IV study, four patients were noted to have ALT levels exceeding three times the higher end of normal.

Conclusion

Thus we conclude that uterine myoma is a common pathology which usually presents with menorrhagia, dysmenorrhagia, pelvic pain, dyspareunia or back pain in Gynaecology OPD, with majority of them responding to medical therapy. On comparing Ulipristal acetate and Mifepristone, it was found that both the drugs were able to significantly improve the PBAC score thereby reducing the amount of blood flow during menstruation and increasing the

haemoglobin levels. Both the drugs were able to bring symptomatic relief in the patients and were able to significantly reduce the size of myoma but the effect of Mifepristone on size reduction was better. After comparing both the drugs on safety profile, the drugs showed reversible proliferative endometrial changes. Ulipristal acetate showed serious reversible liver injury in one case. Hence in our study Mifepristone was found to be better in medical management of myoma however larger study population with prolonged or multiple treatment cycles are suggested for better comparison.

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