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To compare efficacy of mifepristone and Ulipristal acetate in the management of uterine fibroids

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Abstract
Background: Uterine fibroids are one of the most common benign uterine tumors seen in females of reproductive age group. The present study was conducted to compare efficacy of Mifepristone and Ulipristal acetate in the management of symptomatic uterine fibroids.
Materials & Methods: The present study was conducted on 80 women with diagnosis of uterine fibroid. Patients were divided into 2 groups of 40 each. Group I patients were given mifepristone 25 mg orally and group II patients received Ulipristal acetate 10 mg.
Results: There were 28 patients in group I and 25 in group II with size less than 3 cm and 12 in group I and 15 in group II with size 3-5 cm. The difference was significant (P<0.05). There was significant reduction in size more in group II patients with size less than 3 cm as compared to group I patients. There was more percentage of patients in group II having reduction in pain and menorrhagia as compared to group II. However, the difference was non- significant (P>0.05).
Conclusion: Authors found that both the agents can be used in management of women with uterine fibroids.

Keywords: Mifepristone, uterine myoma, Ulipristal

Introduction
Uterine fibroids are one of the most common benign uterine tumors seen in females of reproductive age group [1]. They either may be completely asymptomatic (diagnosed incidentally while doing ultrasound for some other reason) or may present as menorrhagia, lower abdominal or back pain, pelvic mass, obstructive uropathy, anemia secondary to blood loss and infertility. In some patient these symptoms may severely affect the quality of life. The incidence of uterine fibroids is variable because most of them are asymptomatic hence remain undetected for years [2].
Ulipristal acetate (UPA) has a licence for use as a form of emergency contraception. Over the last 6 years, this has been extended to also cover uterine fibroids in women with uterine fibroids associated with heavy menstrual bleeding, or with other moderate or severe symptoms (bulk symptoms, pelvic pain, decreased quality of life [QOL]). Oral contraceptives, progestins and levonorgestrel-releasing intrauterine systems (LNG-IUS) may be used 'off label' to treat women with gynaecological bleeding disorders, but they are not indicated for management of uterine fibroids, because fibroids are progesterone sensitive [3].
Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to estrogen receptors and upregulates androgen receptors. In a placebo controlled trial low dose mifepristone (RU 486) has been shown to decrease myoma size as well as symptoms [4]. Reduction in size with mifepristone might 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 antiproliferative effects [5]. The present study was conducted to compare efficacy of Mifepristone and Ulipristal acetate in the management of symptomatic uterine fibroids.

Materials & Methods
The prospective study was conducted in the Department of Obstetrics & Gynaecology of Acharaya Shri Chander Institute of medical sciences, Jammu. It comprised of 80 females with diagnosis of uterine fibroid.

Written informed consent was obtained from all patients prior to their enrollment in the study. Patients were divided into 2 groups of 40 each. Group I patients were given mifepristone 25 mg orally and group II patients received Ulipristal acetate 10 mg. Females of reproductive age group diagnosed to be having uterine fibroids, Patients having symptoms like menorrhagia, dysmenorrhea, abdominal pain or any other symptoms related to fibroids were included in the study. Exclusion criteria comprised of Pregnant females, those who refused consent, Renal or hepatic dysfunction or any other disease in which either mifepristone or Ulipristal is contraindicated, patients having adenomyosis, endometrial hyperplasia or genital tract infections, not taken any previous medication.

General information such as name, age etc. was recorded. A thorough clinical examination was done. The parameters like change in fibroid size, reduction in pain, resolution of menorrhagia and improvement in quality of life was recorded. Transabdominal or transvaginal ultrasound was done for the diagnosis of uterine fibroid depending upon the size of fibroid and marital status of the patients. Out of the studied case patients 50% patients had subserosal fibroids while 25% and 25% patients had intramural and submucosal fibroids respectively. Patients were followed up for 3 months. Results thus obtained were subjected to statistical analysis. P value less than 0.05 was considered significant.

Results

Table 1: Distribution of patients

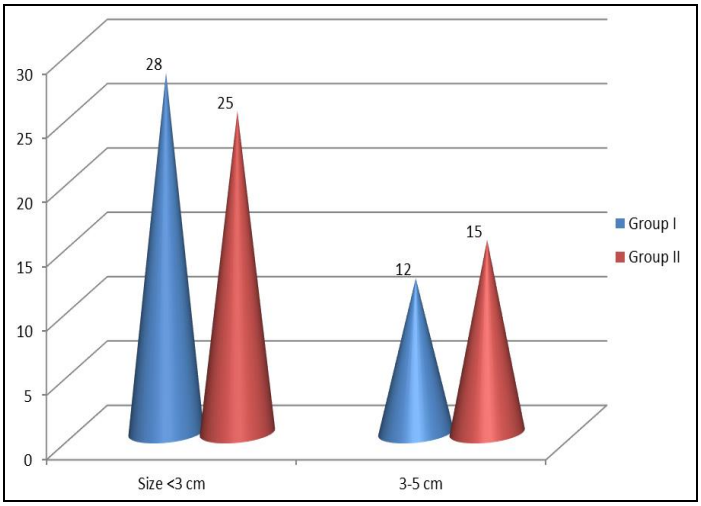
Groups	Group I	Group II
Drug	25 mg mifepristone orally	10 mg Ulipristal acetate
Number	40	40

Table 1 shows that group I patients were given mifepristone 25 mg orally and group II patients received Ulipristal acetate 10 mg.

Table 2: Comparison of size in both groups

Parameters	Group I	Group II
Size <3 cm	28	25
3-5 cm	12	15

Table 2, graph 1 shows that there were 28 patients in group I and 25 in group II with size less than 3 cm and 12 in group I and 15 in group II with size 3-5 cm.



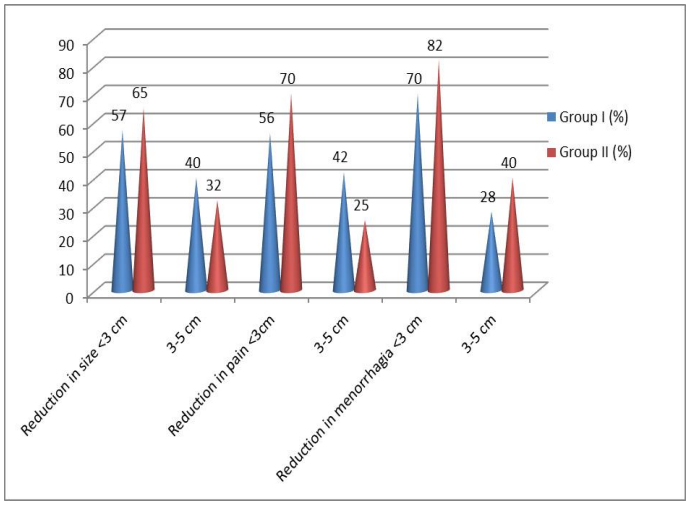
Graph 1: Comparison of size in both groups

Table 3: Assessment of size, pain and menorrhagia in follow up

Parameters		Group I (%)	Group II (%)	P value
Reduction in size	<3 cm	57	65	0.05
	3-5 cm	40	32	
Reduction in pain	<3cm	56	70	0.12
	3-5 cm	42	25	
Reduction in menorrhagia	<3 cm	70	82	0.25
	3-5 cm	28	40	

After 3 months follow up, 2 patients in Group I (both with fibroid size <3 cm) and 3 patients in Group II (one with fibroid size <3 cm and two with fibroid size 3-5 cm) lost in follow up.

Table 3, graph 2 shows that there was significant reduction in size in group II patients with size less than 3 cm as compared to group I patients whereas it was more in group I with size 3-5 cm. There was more percentage of patients in group II with size <3 cm having reduction in pain and menorrhagia as compared to group II whereas reduction in pain was more with size 3-5 cm in group I. However, the difference was non- significant (P>0.05).



Graph 2: Assessment of size, pain and menorrhagia in follow up

Discussion

Uterine fibroids are benign uterine smooth muscle tumors that are present in up to 8 out of 10 women by the age of 50. Many of these women experience symptoms such as heavy and irregular menstrual bleeding, early pregnancy loss, and infertility [6]. Traditionally believed to be inert masses, fibroids are now known to influence endometrial function at the molecular level. 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 antiproliferative effects on endometrium and myometrium [7]. The present study was conducted to compare efficacy of Mifepristone and Ulipristal acetate in the management of symptomatic uterine fibroids.

In present study, there were 80 patients. Group I patients were given mifepristone 25 mg orally and group II patients received Ulipristal acetate 10 mg. Feng *et al.* [8] first described use of mifepristone for the treatment of uterine fibroid. They showed uterine fibroids to be steroid hormone dependent tumors possessing Estrogen and progesterone receptors (ER and PR). They proposed that antiprogesterone reduce the size of uterine fibroids either by blocking the effect of progesterone or interference of estrogen action on fibroids.

We found that there was significant reduction in size more in group II patients with size less than 3 cm as compared to group I patients. There was more percentage of patients in group II having reduction in pain and menorrhagia as compared to group II.

Divaker *et al*. [9] conducted a study in which a total number of 40 patients were recruited in the study of which they were divided into two groups according to the size of the fibroid as <3cm and 3-5cm as seen on transvaginal as well as transabdominal ultrasound. Further they were randomly assigned to either mifepristone or ulipristal orally with each category having 10 patients each to assess changes in fibroid size, in symptomatic pain reduction, menorrhagia and in quality of life. The 25-mg dosage of Mifepristone is shown to be a good and effective way of treatment in fibroids less than 3 cm in achieving 40% reduction in size and 50% reduction in menorrhagia as compared to Ulipristal 10 mg which acts better in other subgroup of size 3-5 cm of fibroids.

Ciarmela *et al*. [10] found that UPA reduces fibroid size by a combination of proliferation inhibition, transitory stimulation of apoptosis and extracellular matrix (ECM) remodelling linked to high matrix metalloproteinase-2 (MMP-2) expression levels, particularly after long-term treatment. During the early phase of treatment, apoptosis is facilitated by temporary repression of survivin, an apoptosis inhibitor. The reduction in fibroid volume is also correlated with high MMP levels and, conversely, low tissue inhibitor of metalloproteinase (TIMP) levels, suggesting that the MMP/ TIMP balance plays an important role in ECM resorption in decreasing fibroid volume. Sustained fibroid shrinkage observed even after treatment cessation might therefore be the result of permanent ECM reduction. In the context of uterine fibroids, UPA does not alter expression patterns of progesterone receptors, nor could their cofactors indicating that the molecular mechanisms involved be more complex than presumed.

Conclusion

Authors found that both the agents can be used in management of women with uterine fibroids. Mifepristone was effective in reduction in size and pain when size of fibroid initially was between 3-5 cm. Ulipristal acetate was effective in decreasing the size and pain when size of fibroid initially was <3 cm and also it is helpful in reducing menorrhagia.

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