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EFFICACY OF USE OF LONG-TERM, LOW-DOSE ULIPRISTAL ACETATE FOR THE TREATMENT OF FIBROIDS

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ABSTRACT

Introduction: Uterine fibroids, also called fibroid tumors, fibromyomas, myofibroma, leiomyofibroma, fibroleiomyoma, myoma, fibroma and leiomyoma, are benign tumors that develop in uterus. This is the most common tumor of the uterus and female pelvis.[1] The incidence is generally cited as 20–25 percent, but has been shown to be as high as 70–80 percent in studies using histologic and sonographic examinations. Majority of fibroids are asymptomatic; however, when symptomatic, patients present with menstrual disturbances, infertility, lump abdomen or pressure effects.[2] Management of fibroids can be surgical or medical. Among the surgical options, hysterectomy is viewed as the definitive management of symptomatic uterine fibroids. Myomectomy is an alternative for patients who desire childbearing, young patients, and for those who prefer to retain the uterus. Medical management may be given to minimize symptoms and signs, and for patients where surgery is contra-indicated. Drugs available are antifibrinolytic-tranexamic acid, danazol, GnRH analogs, progestogens and the antiprogesterone Ulipristal Acetate. Ulipristal Acetate, an antiprogesterone was approved by FDA on September 28, 2000, with the trade name 'Mifegyne' as an abortifacient. The immune reactivity of progesterone receptors in the myoma and myometrial tissue was decreased significantly by this drug, suggesting the regression of these tumors may be obtained through a direct antiprogesterone effect. Varying dosage regimens have been suggested for treatment of fibroids though consensus is for a dose between 5 to 10 mg daily. Higher doses have not shown any increase in the beneficial effect while the side effects have been found to increase.[3] We studied the effect of Ulipristal Acetate given once a week on uterine fibroids for 6 months. The available literature predominantly has studied effects of 3 months exposure with this drug, but in this study, we decided to study the effects of this drug when used for 6 months.

KEYWORDS: Uterine fibroids, also direct antiprogesterone effect.

MATERIALS AND METHODS

The study was designed as an observational prospective "before–after" study. A total of 36 patients were enrolled. Sample size was calculated to study changes in various parameters after 6 months treatment with Ulipristal Acetate 5 mg once a day with the following specifications.

1. H_0:$\mu d = 0$, H_1:$\mu d \neq 0$, $I\mu I = 63.1$.
2. Level of significance = $\alpha = 5$ %.
3. Power of study = $1 - \beta = 80$ %.

Mean and range as per the available literature are tabulated in Table 1.

Table 1: Mean and range as per the available literature.

Mifepristone treatment	Mean fibroid vol.	Range	Mean change
Before	176.8	5.4-923	63.1
After	113.7	0.52-689	

The expected mean reduction in fibroid size was taken to be 40% and SD 24%. Thus, the calculated sample size was 36. A total of 40 patients were recruited, of which 36 satisfied the inclusion/exclusion criteria. Inclusion criteria were fibroid size of 2.5 cm and above, those giving consent to be part of the study, reproductive age-group infertile patients or premenopausal patients, those accepting the use of barrier contraceptive during the period of the study, agreeing to have ultrasound examination at every follow-up or evaluation visit, agreeing to two endometrial biopsies—one before starting treatment and another within 10 days following

treatment termination. Patients who were keen to become pregnant, breastfeeding patients, those on hormonal contraception or who had received any hormonal therapy in the last 3 months, any contraindications to receiving antiprogestins, adrenal insufficiency by history, sickle-cell disease, active liver disease (liver function tests greater than 1.5 times upper range of normal), severe respiratory disease (SpO_2 < 92%), renal disease (serum creatinine >1.5 mg/dl), coagulation defect (abnormal PT and PTT), thromboembolic disease (history of deep vein thrombosis or pulmonary embolus in the past) and those who refused to give consent were excluded from the study.

Permissions from institutional ethical committee were obtained. An informed consent was obtained from all the participants enrolled in the study. Baseline investigations were performed on all patients, which included CBC, LFT, RFT and thyroid function tests. Endometrial biopsy was done premenstrually to rule out endometrial hyperplasia, and transvaginal sonography was done to accurately document myoma volume. Menstrual blood loss was assessed using pictorial blood assessment chart (PBAC) scoring system.

The commercially available tablet of 5mg was given to patient. The patients were asked to take the drug for 6 months totally and called for review in the OPD at 1, 6 and 9 months. In the event of any adverse effects, they were told to stop the drug immediately and report to emergency unit/OPD. The patients were briefed about the possible side effects. They were also further followed up till 3 months after stopping the drug to observe the changes in menstrual pattern, fibroid volume, Hb and LFT. All patients were advised to use barrier contraception to avoid an inadvertent pregnancy. Patients who turned amenorrhoeic, were asked to report to the OPD where pregnancy was ruled out using urine βHCG. An endometrial biopsy was repeated at 6 month of therapy to rule out drug-induced hyperplasia.

RESULTS

Demographically, majority of patients fell in 41–45 years age-group. Fifty percent were Para 2 (18 out of 36). The dominant symptom of our study group was menorrhagia associated with dysmenorrhea and pelvic pain. Seven out of 36 (19.4%) of the patients initially presented with infertility as their main complaints and on further asking reported associated menorrhagia and dysmenorrhea (Table 2).

Table 2: Characteristics of symptoms of patients.

Symptoms	Before treatment (%)
Menorrhagia	32/36 (88.89 %)
Dysmenorrhea	32/36 (88.89 %)
Pelvic pain	34/36 (94.4 %)
Backache	10/36 (27.8 %)
Urinary complaints	3/36 (8.3 %)
Infertility	7/36 (19.4 %)

It was observed that after 6 months of treatment with Ulipristal Acetate, the mean fibroid volume reduced from 204.33 to 113.16 cm^3 (n = 33); $p \leq 0.001$ and the percentage mean volume reduction of the fibroid in the study population was 44.57 % (range 1.10–100 %). However, at 9 months, the mean fibroid volume increased from 108.02 to 114.72 cm^3 (n = 31); p value = 0.129, which was not statistically significant (Table 3).

Table 3: Mean fibroid volume changes.

Parameter studied	*N*	Mean	SD	*p* value
Fibroid vol.				
Baseline	33	204.08	135.63	<0.001
6 month	33	113.16	84.10	
Fibroid vol.				
6 month	31	108.02	82.98	0.129
9 month	31	114.72	98.39	

In the study population, immediate reduction in bleeding was observed in 100 %, and 88.89 % (32/36) patients attained amenorrhea. There was an improvement in general health and a feeling of well being primarily related to decreased menstrual blood loss and improvement in Haemoglobin. The mean Haemoglobin improved from 9.18 to 10.82 g/dl; p = 0.001 (n = 33), which was statistically significant. Subsequent follow-up at 9 months showed mean Hb increased from 10.70 g/dl at 6 month to 10.83 g/dl; $p \leq 0.001$ (n = 31).

Mean hemoglobin changes Due to the antiprogesterone effect, an estrogen-dominant hormonal milieu is created at the endometrium, thereby causing endometrial changes following treatment with Ulipristal Acetate (Table 4).

Table 4: Effect on endometrium after treatment.

Effect on endometrium after treatment Endometrium	Before treatment (n = 36)	After treatment (n = 33) at 6 month
Normal	35 (97 %)	3 (9 %)
Atrophic	–	2 (6 %)
Disordered proliferative	1 (3 %)	26 (79 %)
Proliferative	–	1 (3 %)
Hyperplasia	–	–
Simple hyperplasia	–	–
Complex hyperplasia without atypia	–	2 (6 %)[a]

[a]One patient opted for surgical therapy and underwent a total abdominal hysterectomy at 9½ month after initiation of the drug. Second patient was put on tab. MPA 10 mg TDS at 6 month after initiation of ulipristal acetate and was kept on follow-up.

Assessment of mean blood loss by PBAC scoring system showed reduction from 111.70 (range 70–150) to 7.12 (range 0–70). Thirty-two out of 36 (88.89%) of the patients at the end of 6 months attained amenorrhea, which is significant ($p \leq 0.001$). As a consequence, the dysmenorrhea and pelvic pain were relieved, and subsequently, the hemoglobin rose, thereby reducing the requirement of blood transfusion.

Within the study period of 9 month, it was observed that there were two treatment failures where we had to resort to surgical treatment. One of the patients desired to conceive and also the volume reduction of the fibroid was minimal, thus she underwent abdominal myomectomy during the study. The size of the fibroid was large (451.09 cm^3 volume) and thus was not amenable to medical therapy. The second had to undergo total abdominal hysterectomy as she no longer desired fertility and symptoms showed no improvement. Histopathology of the specimen showed adenomyosis. The literature review also showed that adenomyosis is poorly responsive to Ulipristal Acetate. One patient showed significant reduction in fibroid volume, but was found to have complex endometrial hyperplasia without atypia on EB. She was given high-dose progesterone for 3 months and was followed up with TVS monthly. She showed a thinned-out endometrium 3 months after stopping Ulipristal Acetate.

DISCUSSION

Ulipristal Acetate as a treatment option for myoma, was first reported by Murphy et al.[3] Current studies support that growth of myoma is dependent on progesterone and therefore antiprogestins (Ulipristal Acetate) and selective progesterone receptor modulators (SPRMs-Asoprisnil/Ulipristal) can be effective in treatment. Several clinical trials have been done since then with doses varying from 5 to 10 mg for 3–12 months.[4] Studies have found that a dose of 2.5 mg is not effective in reducing the myoma volume, but a dose as low as 5 mg per day and maximum as high as 5 mg per day was found effective.[4, 5] In the present observational prospective "before–after" study, 50 mg Ulipristal Acetate given once a week was used for 6 months. The rationale of this dose was for ease of administration considering the tablet size commercially available, as well as to improve patient compliance with the once a week, Sunday-to-Sunday schedule. No other study has used this dose of 5 mg Daily. All studies reviewed suggest a daily dose regimen. The first dose was started within first 7 days of menstrual cycle. The drug was started once the endometrial biopsy report and pre-treatment investigations were available. It is known that if the drug is given in the early follicular phase, it starts acting before the development of the dominant follicle, and if given in the late follicular phase, it leads to collapse of the dominant follicle and withdrawal bleeding. Ulipristal Acetate also caused significant improvement in leiomyoma-related symptoms. Mean blood loss (MBL) declined in 100% of our patients. Of these, 88.89% became amenorrhoeic and the rest showed a decreased MBL. However, MBL started increasing when observed at 9 months. Mean PBAC score reduced from 111.70 to 7.12 in the present study at 6 month. Kulshrestha et al.[8] found mean PBAC score reduced from 253 to 19.8 in 2.5 mg daily group and 289.2–10.4 in 10 mg group. In the present study, the change in fibroid volume showed a significant reduction of 44.57 % in fibroid volume at the end of therapy. The further follow-up at 3 months after cessation of therapy showed no further reduction. This suggests no residual effect of the drug. However, the lack of immediate increase in size of fibroids after stopping the drug also suggests that the progesterone receptors take some time to recover from the blockage by Ulipristal Acetate before regrowth occurs. A total of seven patients had infertility as a presenting complaint in the study. Of these, one had primary infertility and six had secondary infertility. All these patients, barring one, had small-sized symptomatic deep intramural fibroids not easily amenable to either hysteroscopic or laparoscopic removal. The rationale for use of this drug in these patients was to try and see if the size of the fibroid would reduce to such a point where it would not be a significant factor causing her symptoms and eventually her infertility. The one patient who had a large fibroid and infertility (volume 451 cm^3) eventually did require a myomectomy.

Endometrial hyperplasia without atypia was found as one of the possible side effect of Ulipristal Acetate therapy. Eisinger et al.[9] concluded that 28% of subjects develop simple endometrial hyperplasia without atypia. However, these drug-induced endometrial changes are reversible as menstruation resumes on cessation of the drug. In the study, two of the patients developed complex hyperplasia of the endometrium without atypia (6% of the study group).

CONCLUSION

Six months therapy with 5mg of Ulipristal Acetate given daily is efficacious and acceptable for the treatment of symptomatic leiomyoma. Although its use as a primary medical therapy is limited due to recurrence after stopping treatment, it can be used especially for perimenopausal women whose myoma would regress after menopause and younger infertile patients with small-size deep intramural myomas not easily accessible to either hysteroscopic or laparoscopic surgery. It can also be beneficial as a preoperative adjunct, in patients with preoperative severe anemia and large fibroids where surgery is technically difficult. Mode of surgery can be changed to a less-invasive vaginal hysterectomy rather than an abdominal procedure.

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