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Original Research Article

Study on Effects of Low Dose Oral Mifepristone on Uterine Fibroids

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Abstract:

Background: The most frequent benign tumors in women and the most common pelvic tumors are uterine fibroids. Fibroids frequently cause pain and abnormal uterine flow as symptoms. The objective of the present study is to evaluate the efficacy and safety of two low doses of mifepristone 10 mg and 25 mg in small (< 3 cm) and big myomas (4-6 cm) respectively.

Methods: A total of 60 patients of reproductive age group with fibroids were divided into two groups: Group I (n=30) included women with fibroid size (4-6 cm) and Group II (n=30) included women with small fibroid size (<3 cm). Group I and Group II were administered daily dose of mifepristone as 25mg and 10mg respectively. Statistical analysis was done using SPSS software.

Results: The results of our study demonstrated that 10 mg of mifepristone is as effective as 25 mg/day dose in relieving menorrhagia and reducing myoma volume. However, effect on pain reduction was slightly more pronounced with 25 mg dose of mifepristone as compared to 10 mg dose. Three patients who did not respond satisfactorily to 10 mg dose in the group 2 were escalated to 25 mg daily dose which improved the myoma symptoms and sustained the results ($p<0.001$). Moreover, there were minimum side effects.

Conclusion: Fibroids, irrespective of the characteristic, whether submucous, intramural or subserous respond very well to mifepristone and disappeared on follow-up on high resolution ultrasound. Twenty-five mg daily dose is preferred over 10mg, irrespective of the size of the fibroid. Mifepristone is an acceptable solution for the medical management of the fibroids upto six cm as it is administered orally, is cost effective with mild side effects.

Keywords: Mifepristone, Fibroids, Leiomyoma.

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Introduction

Leiomyoma is the most common benign uterine neoplasms of fibromuscular tissue with an incidence of 20-40% in women of reproductive age group and over 40% in women more than 50 years age. [1] Fibroids are the leading cause for hysterectomy, making this surgery the third most common surgical in tervention worldwide. [2,3]

However, for the woman who desires future fertility or is apo or surgical candidate, definitive management with hysterectomy is not the line of treatment. Moreover, in developing countries such as India there is a rise in unnecessary hysterectomies that impose financial burden to the family. [3] Medical management of fibroidis an alternative for women unsuitable for hysterectomy. Drugs used for the treatment of fibroid aimed at reducing tumor burden by dissolution of the aberrant extracellular matrix. [4]

New concept substantiates the fact that progesterone plays a key role for maintenance and growth of uterine leiomyoma and estrogenis required only for up regulation of progesterone receptors. [5] Others studies haves shown that Progesterone receptors are elevated within leiomyoma, as compared against adjacent myometrium. [6,7] Taken together, these points make Selective progesterone receptor modulators (SPRMs) to emerge as a valuable treatment option for uterine fibroids, which offer potential for long term medical treatment and there by patients may avoid surgical intervention. [8] Mifepristone is

the first and one of the most widely used SPRMs with mixed agonistic/antagonistic properties and tissue-specific effects. It was first developed in 1980 and first came into clinical use (marketed) in France in 1987. [9] Murphy et al (1993) first studied mifepristone, for the treatment of leiomyomas. [10] The clinical benefits of mifepristone in the treatment of myoma is at tribute to (a) Antiproliferative and proapoptotice effects on leomyoma cells, (b) Ovulation inhibition which causes amenorrhoea, (c) Suppressive effects on stromal vasculature and reducing stromal vascular endothelial growth factor, (d) Decreases the production of protein in the extracellular matrix of leiomyoma. The objective of the present study is to evaluate the efficacy and safety of two low doses of mifepristone 10mg and 25mg in small (<3cm) and big myomas (4-6cm) respectively.

Materials and Methods

This was a one year prospective study on women with fibroids from July 2023 to December 2023.The study was conducted at Department of Obstetrics and Gynaecology, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar.

The study included 60 patients of reproductive age group suffering from leiomyoma either with single or multiple fibroids. All the three subtypes of fibroids i.e. submucous, intramural and subserous were included in the study. Informed consent was obtained from all participants. Patients with symptomatic and confirmed cases of fibroids, normal Pap smear, non-hormonal contraception, good compliance and no emergency indication for any action or surgery were included in this study. Patients with asymptomatic and any other causes of symptoms, abnormal Pap smear, hormonal contraception, active genital Infection, pregnancy and breast feeding, hepatic or renal dysfunction and no contraindication or drug interaction were excluded in this present study.

These patients were divided into two groups depending on the size of fibroids.

Group I (n=30) included women with leiomyoma of size 4-6 cm. Mifepristone was administered orally at a dose of 25 mg daily for a period of three months.

Group II (n=30) included women with leiomyoma of size <3 cm. Mifepristone was administered orally at a dose of 10 mg daily for a period of three months.

There was an open scope to up titrate the dose of mifepristone to 25 mg daily in non- responders. Complete baseline clinical profile including details of menstrual cycle, symptoms and their severity was noted. The primary outcome of the study considered for efficacy was menstrual bleeding. Secondary outcomes of the study were severity of pain, general well-being of the patients and reduction in the volume of leiomyoma.

The amount of blood loss and clots were assessed by Pictorial blood loss assessment chart (PBAC) and scores. It is a semi- quantitative assessment that takes into account the number of pads soaked, their degree of soakage, passage of clots and episodes of flooding. A score of more than 100 is labelled as a case of menorrhagia. [13] Verbal pain intensity scale (VPIS) was used for pain, dysmenorrhea, dyspareunia, pelvic pain, in which patients were asked to describe their pain on a scale of 0 to 10 from no pain to worst ever pain. A complete general and gynaecological examination was done. Tests were done for haemoglobin estimation, coagulation profile, liver, kidney and thyroid function tests.

Volume of each myoma was calculated and added in cases of multiple myomas. Fibroid volume and the uterine volume were calculated by the formula V= 0.5233 (D1XD2XD3) where D1, D2 and D3 are longitudinal, transverse and cross section diameter of the fibroid. Transvaginal USG was done in cases of polyps and submucous myomas. Endometrial biopsy was done in those with endometrial hyperplasia and who consented for the same.

All patients were followed up monthly for three months for changes in their symptoms, bleeding patterns, PBAC score and VPIS score. Ultrasound was repeated on each clinical visit to note the size of the fibroids and any other pathology. Patients were followed up after six months (three months of treatment completion), they were asked about their symptoms and repeat ultrasound was also done for the size and number of fibroids, uterine volume and endometrial thickness.

Three patients did not respond as expected with the dose of 10 mg/day and were up titrated with the dose of 25 mg/day for the fourth month, and response was calculated. Haemoglobin estimation with liver function tests were repeated after three months of treatment.

Data for all quantitative variables are presented as mean±standard deviation. Parameters for safety or complications were analysed on the basis of actual treatment received. Statistical analysis was done by SPSS.

Results

A total of 60 patients (30 in each group) were enrolled at Gynae Outpatient Department and followed up for three months after taking informed consent. All the patients in both the group completed the study.

Table1: Baseline characteristics of the two groups

Parameters	Group1(n=15)	Group2(n=15)
Age(years)	39.8±5.15	37.4±8.38
PBAC Score	292.87±80.22	225.47±79.18
VPI Score	4.53±1.92	4.27±1.83
Myoma volume(cm^3)	39.69±47.72	7.49±3.43
Uterine volume(mm^3)	378.31±258.07	207.98±89.26
Endometrial thickness(mm)	7.45±1.89	8.64±2.34

The mean PBAC score at enrolment was 292.82 in group1 and 225.47 in group 2 patients. The reduction in PBAC score was statistically significant as compared to the baseline in both the groups ($p<0.001$). The results were remarkable from the first month of the initiation of the treatment and there was complete cessation of the menstrual cycles by the third or fourth week of the treatment in all the patients. The menstrual cycles were restored in average 45 days in group 1and 43 days in group 2 after completion of treatment, which were absolutely normal.

The mean VPIS was 4.53 ± 1.9 in group 1 and 4.27±1.83 in group 2 patients with marked relief and significant decrease in VPIS score in both the groups, p value<0.001. The percentage decrease was 58.82% after one month and 88.23% after second month of therapy in group 1. The percentage decrease was 68.75% after one month and 96.8% after second month of therapy in group2.

The mean myoma volume was 39.6 cm^3 in group 1 and 7.49cm^3 in group 2. There was a significant decrease in the myoma volume of both the groups, p value<0.001. In thegroup1, 81.36% reduction in the myoma volume (in3months) was observed as compared to the baseline and similarly, group 2 demonstrated 81.0% reduction.

The myoma volume when compared between single versus multiple myomas, after three months of mifepristone therapy resulted in 85.08% reduction compared to 79.11 % reduction in single myomas. We demonstrate that there is a relatively better response in patients with multiple myomas and the improvement was sustained and did not revert back even after three months of cessation of the therapy. When the comparison was done in group1 andgroup2, multiple myomas responded better than single fibroids in the group 1 (25mg).

Uterine volumes, before the start of the treatment, in both the groups were 378.31 mm^3 and 207.98 mm^3 respectively. After three months, the volumes were significantly reduced to 190.8 and 147.73 mm^3 respectively (p value<0.001) There was 49.55% decrease in the group 1cases and 28.96% reduction in group 2 patients. This reduction was maintained even after three months of stopping the therapy, which demonstrates the delayed the rapeutic benefits of our approach. The mean endometrial thickness before the initiation of treatment in both thegroups was 7.45mm and 8.6mm respectively. After three months of therapy, thickness was 8.04 and 8.60 respectively which was numerically superior but statistically insignificant.

Mean haemoglobin levels in both the groups at the initiation of the treatment were 9.34 and 10.14gm% respectively. The rise in the haemoglobin levels was statistically significant, as compared to the baseline, in both the groups after three months without giving any hematinic ($p<0.001$). The levels in both the groups were 11.08 and 11.66gm% after three months. The haemoglobin levels showed 15.6% rise in group 1 and 14.9% rise in group 2 patients.

There was no alteration in the coagulation profile, liver, kidney and thyroid function tests.

Discussion

Progesterone receptor modulators have shown efficacy in several studies for the treatment of gynaecological problems such as myoma, endometriosis and abnormal uterine bleeding. [14,15] It is a cost-effective therapy for the treatment of fibroid. Various studies have evaluated mifepristone in a varying dose of 2.5 to 50 mg/day for a period of three to six months and were found to a melioratеleiomyoma related symptoms, reducing the myoma volume by 26 to 57% and inducing a menorrhea in 46 to 100% cases. [16,21] Ultralowdoseofmifepristone2.5mgalsoresultedinappreciable symptomatic relief, modest reduction in uterine volume, thus suggesting a good possibility of improvement in the quality of life. [22]

The results of our study also demonstrated that 10 mg of mifepristone is as effective as 25 mg /day dose in relieving menorrhagia and reducing myoma volume. However, effect on pain reduction was slightly more pronounced with 25 mg dose of mifepristone as compared to 10 mg dose. These results are in contrast to the previous studies where 10 mg of mifepristone was found to be as effective as 25 mg in relieving menorrhagia, pain and other myoma related symptoms, while size reduction was more with 25 mg dose.

The small size of the present study may be the reason for such results. Also, effect on single myoma is almost same with both the doses but when we compared the effect on multiple myomas, 25 mg dose showed more response than 10 mg

dose. Similar results have been documented in a prospective randomized clinical trial by Engman et al. As reported in previous studies, improvement in the myoma symptoms was noted from the first month of therapy.

Symptomatic relief persisted for three months after cessation of treatment. [20] A little increase in the PBAC score was noticed during the follow-up period but was much lower than the initial levels. Uterine volumes reduced more prominently after three months. [21]

One patient remained asymptomatic even eight months later with no increase in fibroid volume which was differentiating from the published literature, where it is expected that fibroid volume starts increasing in due course of time, after the therapy stops. We postulate that the prolonged residual effect may be due to time lag taken for the normalization of the progesterone receptors. One infertile patient conceived after stopping the treatment, indicating that fertility resumes soon after cessation of mifepristone.

The unopposed estrogenic effect on the endometrium by Mifepristone would account for the marginal increase in the endometrial thickness on treatment. However, once the treatment was stopped, it normalized. We had excellent compliance of the patients may be due to fast and absolute symptomatic relief to the patients.

Also, we had almost negligible side effects, may be because of the low doses and shorter duration of treatments.

In the group 2 patients, out of the thirty patients who were administered 10 mg/day for 3 months, the response in the three patients was suboptimal and they consented for the trial of higher dose of 25 mg/day for one more month. This resulted in the remarkable response in the reduction of myoma volume without any added side effect and yielded greater satisfaction to the patients, thus proving the better efficacy of 25 mg/day dose over 10mg/day dose in smaller leiomyomas.

Ulipristal acetate has shown similar efficacy at the dose of 5-10 mg/day as 91-92% reduction in menstrual blood loss, amenorrhea in 75-83% of cases and 12-20% reduction in myoma volume. [14] Unfortunately, in February 2018, the Medicines & Healthcare products Regulatory Agency issued a safety alert for ulipristal acetate due to reports of serious liver injury in women using the medication for uterine fibroids. Five reports of serious liver injury, including four cases of hepatic failure needing transplantation, have been reported.

Conclusion

Thus, were commend that mifepristone in low dosesof1 0 and 25 mg has excellent patient satisfaction rates, and better powered randomized clinical trials should be conducted to define the duration of therapy.

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