

Mifepristone in Fibroids: An Alternative!

¹Sunita Lamba, ²Aabha Singh, ³Priyankur Roy, ⁴Ruchika Garg

ABSTRACT

Introduction: Medical management is a keystone in managing symptomatic fibroids. Availability of an effective, safe, and cost-effective medical treatment should always be considered as an alternative to reduce the cost, morbidity, and impact of avoidable major surgeries.

Objective: To study the effect of 10 mg Mifepristone on symptomatic fibroids.

Materials and methods: This prospective study was conducted at a tertiary care center in Raipur. Fifty women of the reproductive age group with symptomatic uterine fibroids with normal liver and kidney function tests were recruited. A total of 10 mg of oral Mifepristone was administered daily for 3 months. Monthly symptomatic assessment, ultrasonography, and biochemical parameters were done to assess changes.

Results: There was significant reduction in menstrual blood loss (MBL) and associated symptoms. Amenorrhea occurred in 100% of women after 3 months of treatment. The fibroid volume and mean uterine size reduced by 26.2 and 26.99% respectively. Mean hemoglobin levels increased by 1.93 gm/dL. Observed side effects were few and tolerable.

Conclusion: Mifepristone is an effective and safe alternative for the management of leiomyoma.

Keywords: Fibroid volume, Leiomyoma, Mean uterine size, Medical management, Mifepristone, Symptomatic fibroids.

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INTRODUCTION

Uterine fibroids are the most common benign tumors of women. They commonly present with menstrual disturbances, pain, pressure symptoms, and fertility problems. The disabling symptoms and absence of effective medical therapy attribute to high rates of surgical management of fibroids. It is a common indication for hysterectomy leading to financial burden. Though minimal invasive methods like uterine artery embolization, high intensity focused ultrasound, and magnetic resonance-guided focused ultrasound are available, still they are beyond the reach of most women due to high expertise required and cost. Medical management like gonadotropin-releasing hormone (GnRH) analog and Danazol are expensive and have a number of side effects. Thus, the search for an acceptable, safe, and effective nonsurgical treatment option for symptomatic leiomyoma is of considerable clinical and public health importance.

Mifepristone is a synthetic derivative of norethindrone with antiprogesterone activity.¹ Various studies have suggested its use in fibroids.² It has been found to improve the quality-of-life in symptomatic women with fibroids.³ Our study was conducted to assess the effects of Mifepristone on symptomatic fibroids and its side effects.

MATERIALS AND METHODS

Fifty women with symptomatic fibroids who presented to the gynecology outpatient department in a tertiary care center in Raipur were included in the study. It was a prospective interventional study. The study was taken up after obtaining Institutional Ethical Committee clearance.

Study Outcome: The present study was designed to evaluate the effectiveness of 10 mg Mifepristone on symptomatic fibroids.

Study Design: Prospective interventional study.

Study Population: All women with symptomatic fibroids, fulfilling the inclusion criteria were enrolled into the study.

Study Period: Two years.

Informed Consent: All the women and the attenders gave written informed consent before administration of Mifepristone.

¹Clinical Fellow, ²Professor, ³Tutor, ⁴Associate Professor

¹Department of Obstetrics and Gynecology, Institute of Kidney Diseases and Research Centre, Ahmedabad, Gujarat, India

²Department of Obstetrics & Gynecology, Pt. Jawahar Lal Nehru Memorial Medical College, Raipur, Chhattisgarh, India

³Department of Obstetrics and Gynecology, North Bengal Medical College & Hospital, Siliguri, West Bengal, India

⁴Department of Obstetrics & Gynecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

Corresponding Author: Sunita Lamba, Clinical Fellow Department of Obstetrics and Gynecology, Institute of Kidney Diseases and Research Centre, Ahmedabad, Gujarat, India Phone: +918740834555, e-mail: sunita.lamba011@gmail.com

Inclusion Criteria

- Women with symptomatic fibroids and willing for regular follow-up
- Women in the reproductive age group.

Exclusion Criteria

- Pregnant women
- Women desirous of pregnancy
- Breastfeeding women
- History of intake of hormonal therapy in the previous 3 months
- Diagnosed or suspected ovarian, cervical, or uterine malignancy
- Presence of medical ailments like liver disorders, renal disorders, heart disease, or adrenal disorders
- Pelvic inflammatory disease or other adnexal pathologies
- Psychiatric disorders
- Sickle cell anemia
- Bleeding disorders
- Woman necessitating early surgical intervention were also excluded.

Informed consent was obtained from all recruited women and their attenders. Women were assessed for fibroid-related symptoms on a visual analog score. Baseline pelvic ultrasound and blood parameters, such as hemoglobin and liver and kidney function tests were done. Women were followed monthly during the treatment period for 3 months. Monthly symptomatic score was done on the visual analog score. Pelvic ultrasound and blood parameters were again repeated after 3 months of initiation of treatment. Side effects were noted. Women were followed up until 6 months for noting any recurrence of symptoms.

Visual Analog Scale used for Symptomatology

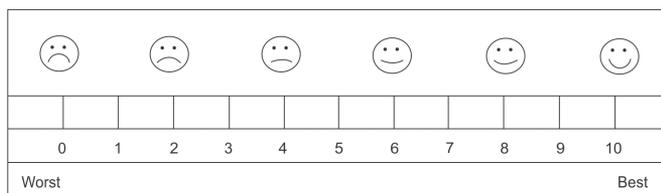


Table 1: Profile of women in the study group

Characteristics	Mean	SD	Range
Age (years)	38.92	5.75	24–48
Parity	2.26	3.34	1–5
Body mass index (kg/m ²)	25.28	3.24	17–32
Uterine volume (cc)	204.03	113.12	85–600
Fibroid volume (cc)	36.56	41.39	4–128

SD: Standard deviation

Statistical Methods

Statistical analysis was carried out using commercial software Statistical Package for the Social Sciences version 20. The descriptive measures like mean, median, and standard deviation for continuous variables were obtained. Frequencies and percentages were calculated for all categorical variables.

RESULTS

All 50 women came for regular follow-up for the entire period of 6 months from the initiation of treatment. The baseline characteristics of women enrolled in the study are shown in Table 1.

The various symptoms of women and their improvement after Mifepristone therapy are shown in Table 2. Severity of the symptoms on visual analog score decreased satisfactorily in the majority of women. Symptomatic relief was significant at end of 3 months. Cessation of the menstruation was the most prominent finding in Mifepristone-treated women. Amenorrhea occurred in 90% of women by the end of first month and 100% of the women at the end of third month of treatment. Due to amenorrhea, 100% of women were relieved of dysmenorrhea completely. Menstrual blood loss decreased significantly (p-value 0.0001) even after 1 month of therapy. About 96% women regained their menses after cessation of drug within 6 weeks. Menstrual blood loss remained significantly low in 87% of women in follow-up until 6 months of initiation of therapy.

In the present study, the mean uterine volume was reduced significantly (p-value 0.006) after 3 months of treatment. Reduction in volume was also achieved in first month (8.93% decrease) and second month (17.41% decrease) of therapy, but it was only significant after 3 months of treatment (Table 3).

Reduction in leiomyoma volume by 26.2% was observed at the end of therapy. However, reduction in fibroid volume was not significant statistically. There was no significant change in endometrial thickness (Table 3). In six women, fibroid volume did not change, but symptomatic relief was present.

Table 2: Distribution of women according to complete resolution of symptoms

Symptoms	Baseline	3 months	6 months
Menstrual disturbances	45	0	6
Dysmenorrhea	38	0	1
Pelvic pain	30	19	14
Backache	18	12	10
Urinary complaints	15	9	5

Table 3: Effect on ultrasound parameters

Parameters	Baseline	At 3 months		p-value
		months	% change	
Uterine volume (cc)	204.03 ± 113.12	148.96 ± 86.88	26.99	0.006
Fibroid volume (cc)	36.56 ± 41.39	26.99 ± 32.91	26.2	0.200
Endometrial thickness (mm)	7.00 ± 2.34	7.19 ± 2.98	2.5	0.722

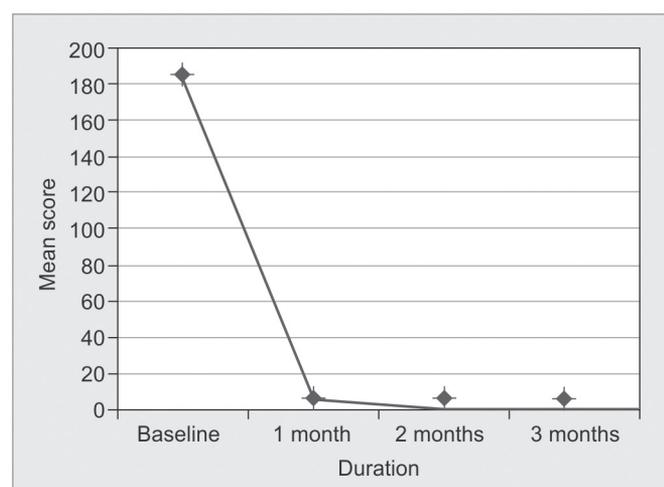
Table 4: Effect on hematological parameters

Parameters	Baseline	After therapy	p-value
Hemoglobin (gm/dL)	9.51 ± 1.31	11.44 ± 0.78	0.0001
Serum bilirubin (mg/dL)	0.38 ± 0.16	0.42 ± 0.16	0.30
Alanine aminotransferase (U/L)	19.4 ± 6.55	19.62 ± 5.64	0.85
Aspartate aminotransferase (U/L)	18.86 ± 6.66	19.9 ± 6.39	0.42
Blood urea (mg)	17.50 ± 7.87	16.76 ± 4.18	0.55
Serum creatinine (mg)	0.85 ± 0.22	0.82 ± 0.13	0.406

Mean hemoglobin level increased by 1.93 gm/dL (p-value 0.001) after therapy. Significant increase was reported even after the second month of therapy. There was no negative effect on renal function tests (Table 4). In three women, mild elevation of liver transaminase was observed at end of 3 months, but was of no clinical significance. Observed values of liver transaminase were 50 to 55 IU in these women (normal value: 46 and 49 IU for the aspartate aminotransferase and alanine transferase respectively).

Other observed side effects included hot flushes, which were noted in 3 (6%) women, and 2 (4%) women complained of mild joint pains. Potential side effects like nausea, vomiting, diarrhea, headache, weight gain, and loss of libido were not seen in the present study.

After completion of treatment, 42 (84%) women remained relatively symptomless until the next 3 months

**Graph 1:** Effect of therapy on MBL on PBAC

of follow-up. The effect of therapy on MBL on pictorial blood loss assessment chart (PBAC) is shown in Graph 1. Other forms of medical management like GnRH analogs were required in three women. Surgical intervention was required in five women. Hysterectomy was performed in three women for recurrence of menorrhagia and in another one woman for persistence of severe dysmenorrhea and pelvic pain. Myomectomy was required in one woman for no significant reduction in the size of abdominal lump.

DISCUSSION

There are various modalities for the management of fibroid uterus like expectant management, medical therapy, conventional surgical options, and newer less invasive approaches. The choice of the procedure depends on many factors including age, parity, fertility, severity of symptoms, size, number and location of fibroids, and desire for uterine preservation.

The present study has shown that 3 months of treatment with 10 mg Mifepristone effectively improved fibroid-associated symptoms, such as bleeding, dysmenorrhea, pain, pressure symptoms, improvement in hemoglobin levels, and reduction in uterine and fibroid size. A 10 mg dose is as effective as 50 mg with lesser side effects.⁴

Mifepristone-induced reduction of menstrual bleeding and increase in hemoglobin level are the most important and useful observations of our study. Amenorrhea, in our study, was observed in 100% women. It was in higher percentage as compared with other studies using similar dose and duration.¹ These results are comparable with higher dose (50 mg) administered for 3 months.⁴ Occurrence of amenorrhea was responsible for improvement of hemoglobin levels. Dysmenorrhea was also relieved completely in all women as a consequence of amenorrhea. In another study, Bagaria et al¹ reported complete relief of dysmenorrhea in 80% of women. Pelvic pain was relieved in 36.6% women in our study. Eisinger et al⁵ reported pain relief in 41.6% women and they used ultralow dose of Mifepristone for 6 months. Prevalence and severity of backache and urinary complaints also decreased with Mifepristone. Similarly, symptomatic relief was reported by other studies.⁴⁻⁶

In our study, there was remarkable reduction in the uterine size and fibroid volume along with symptomatic response. Shikha et al⁷ showed 3 months treatment of 25 mg Mifepristone effectively controls bleeding, reduces the uterine and myoma volume, and thus, can help avoid blood transfusion and hysterectomy in a number of symptomatic myoma cases. Symptomatic

relief and reduction in size were less when dose of drug was reduced below 10 mg.⁶ Kulshrestha et al⁸ proved that Mifepristone (10 and 25 mg) caused symptomatic relief with more than 90% reduction in MBL. Greater myoma size reduction occurred with 25 mg dose. Amenorrhoea was developed in 90 to 95% patients, which was reversible.

After treatment, 1.93 gm/dL rise in hemoglobin level was noted. Improvement in hemoglobin was also reported in other studies.^{1,4} Elevation of liver transaminase was observed in three women (6%) and was comparable with the results of other studies.² This minimal elevation had no clinical significance. Bagaria et al¹ did not report any alteration in liver enzymes. Kidney function tests remained unaltered.

Hot flushes were observed in three women and joint pain in two women. These side effects were relieved after stoppage of the drug. Carbonell et al² also reported side effects in their study. In two Indian studies, no general side effects were reported.^{1,6} This short-term treatment with Mifepristone in our study was well tolerated and no serious side effects were noted.

CONCLUSION

Mifepristone can be considered as an effective alternative for management of fibroids. Lack of general and biochemical side effects together with excellent symptomatic relief confirm its suitability for management of fibroids and reducing major surgical procedures. However, long-term, large multicentric randomized

controlled trials are required to decide dose, duration, long-term safety of drug and its effect on fertility.

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