ORIGINAL ARTICLE

Effectiveness of Low Dose Mifepristone in Medical Management of Fibroids

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Abstract

Introduction: Uterine fibroids can adversely affect the quality of life of women of reproductive age. Symptomatic fibroids are managed medically or surgically. Medical treatment of fibroids includes selective progesterone receptor modulators (SPRM) like ulipristal and mifepristone and GnRH analogs, which reduce bleeding and inhibit the growth of Leiomyoma. At present, ulipristal and GnRH analogs are available in India for medical management which are expensive and associated with side effects which precludes their long use. Mifepristone is used as an off-label indication in medical management of fibroid. This study was conducted using 5 mg dose to see efficacy in reducing blood loss in symptomatic fibroids and associated side effects.

Materials and methods: A single arm interventional clinical trial was conducted at a tertiary Government Hospital in New Delhi enrolling 70 women aged 14–49 years, having fibroids causing heavy menstrual bleeding (AUB-L). Uterine size >14 weeks, suspected or confirmed uterine malignancy and those with severe medical disease were excluded. Study participants were given 5 mg oral mifepristone daily for 3 months. The primary outcome studied was reduction in uterine bleeding measured by pictorial blood loss assessment chart (PBAC) at 1, 3, and 6 months. Reduction in fibroid size, uterine volume, and endometrial thickness was measured by ultrasonography at 3 months. Side effects were noted and at 6 months of enrollment PBAC was further assessed for any residual effect.

Results: A total of 49 (70%) and 55 (78.5%) women were found to be amenorrheic after 1 and 3 months of starting mifepristone, respectively. After 3 months, there was a statistically significant improvement of 21.6% in hemoglobin ($p < 0.0001$). There was statistically significant reduction in fibroid and uterus volume ($p = 0.005$ and 0.046, respectively). No significant change in endometrial thickness was noted. The side effects reported were minor.

Conclusion: Low-dose mifepristone can be considered as an effective, safe, and cheap alternative for medical management of myoma-related abnormal uterine bleeding as well as for preoperative correction of anemia.

Keywords: Fibroids, Fibroid volume, Heavy menstrual bleeding, Leiomyoma, Medical management of fibroids, Mifepristone, Selective progesterone receptor modulators.

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Introduction

Uterine leiomyoma are the most common benign pelvic tumors with prevalence of 80% in women respectively by age of 50.[1] Approximately 30–40 % are symptomatic and require treatment.[2] The symptoms include heavy menstrual bleeding (HMB), dysmenorrheal, pelvic pain, and pressure symptoms depending on the location and size of fibroids. Symptomatic fibroids are managed medically or surgically. Medical treatment of fibroids includes selective progesterone receptor modulators (SPRM) like ulipristal and mifepristone and GnRH analogs, which reduce bleeding and inhibit the growth of leiomyoma. At present, ulipristal and GnRH analogs are available in India for medical management which are expensive and associated with side effects which precludes their long use. The present study, which is a pilot study using low dose 5 mg, was conducted to evaluate the effectiveness and side effects of Mifepristone in the management of symptomatic fibroids.

Materials and Methods

A single arm, interventional short-term clinical trial was conducted in the Department of Obstetrics and Gynecology in a tertiary level teaching Government Hospital, New Delhi, from September 2020 to October 2022. The study was registered in Clinical trial registry of India (CTRI Ref/2021/01/039808). Seventy females in the age-group of 14–49 years attending Gynecology Outpatient Department at RML Hospital and having fibroids causing HMB defined as pictorial blood loss assessment chart (PBAC) score >100 were enrolled for the study. Women with fibroid size >3 and <8 cm and uterine size up to 12–14 weeks were included. Pregnant or lactating women, known hypersensitivity to mifepristone, history of thromboembolic disease/coagulation defect with severe hepatic impairment, severe respiratory, and liver disease were excluded from the study.

A detailed history and thorough general physical and gynecological examination was done for all study participants. Menstrual blood loss was quantified using PBAC score. The study

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subjects underwent a baseline biochemical evaluation including complete blood count, liver function test, renal function test, and TSH. Besides this, a transabdominal/transvaginal ultrasound was done for all cases. During ultrasonography, we recorded volume of uterus; number, size, location and volume of fibroids and endometrial thickness. The commercially available tablet is in strength of 25 and 200 mg. Patients in the study were given oral solution of mifepristone which was prepared by mixing two tablets of 25 mg mifepristone (50 mg) in 100 mL of sterile distilled water. Thereafter, patients were advised to take 2 tea spoon (10 mL) of solution (= 5 mg mifepristone) once daily for 90 days from second day of menstruation. All the patients were followed up monthly for 3 months and then at 6 months post-treatment. They were advised to report in case of any allergic reaction or side effects. At each follow-up visit, study subjects were enquired about side effects, any symptomatic improvement and PBAC scores were calculated. Monthly clinical examination as well as HB, LFT, and KFT were done. The primary outcomes was reduction in uterine bleeding measured by PBAC at 1 and 3 months and at 6 months. Secondary outcome was reduction in size of fibroid and uterus measured ultrasonically and presence of side effects at 1 and 3 months of treatment. The 6 month follow-up was done to see any cumulative effect of Mifepristone.

Definitions Used

Success of treatment was defined as number of patients having more than 50% reduction in PBAC at the end of 3 months of mifepristone treatment.

Treatment failure was defined as no improvement or worsening of PBAC anytime during 3 months of treatment.

Major adverse side effects were defined as any derangement of LFT or KFT or potential life-threatening event attributed to mifepristone during 3 months of treatment.

Statistical Analysis

The data normality was checked by Kolmogorov–Smirnov test. The cases in which the data were not normal, non-parametric tests were used. Quantitative and not normally distributed variables were analyzed using Wilcoxon signed rank test and Friedman test followed by *post hoc* analysis by Dunn's multiple pair-wise comparison test. Variables which were quantitative and normally distributed were analyzed using paired *t* test. Analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 25.0. For statistical significance, p-value < 0.05 was considered statistically significant.

Observations and Results

Out of the 70 women enrolled for the study, 62 patients (88.57%) completed the 3 months treatment. The dropout rate was seen in 3 (4.28%) and failure rate was seen in 5 (7.14%) in the 70 patients enrolled. Mifepristone was effective in reducing bleeding in 62 out of 67 (92%) patients at the end of 3 months.

There were eight (11.4%) patients who did not complete 3 months of treatment, out of these three were dropouts and five were failures. Two patients (2.85%) discontinued the treatment in the first month itself, due to unacceptable side effects of palpitations and raised transaminases, respectively. One patient (1.42%) had continuous bleeding in the first month despite mifepristone and underwent surgery. Two patients (2.85%) did not have any symptomatic improvement and had surgical treatment after 2 months of mifepristone.

Table 1: Comparison of PBAC scores at enrollment, at 1 month, at 3 months, and at 6 months of mifepristone

PBAC score	*Median (25th–75th percentile)*	*p-value*
At enrollment	222.86 ± 64.59	
At 1 month	24.21 ± 64.41	<0.0001
At 3 months	14.13 ± 53.33	<0.0001
At 6 months	245.32 ± 64.55	<0.0001

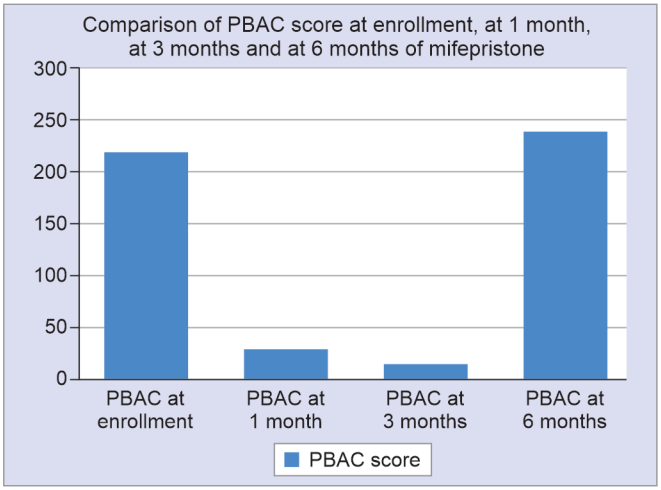

Fig. 1: Effect of mifepristone on PBAC score at enrollment, at 1 month, at 3 months, and at 6 months

Demographic Variables of the Study Population

The mean age of the study participants was 41.39 ± 6.4 years. While their age ranged from 25 to 49 years, majority (62.77%) of the women belonged to age-group of 41–49 years. Four patients (5.7%) were in the age-group of 21–30 years, 22 (31.4%) were in the age-group of 31–40 years, and only three patients (4.2%) were in the age-group of 51–60 years. Five (7.14%) of the participants were unmarried. Four (5.7%) and forty-nine (70%) study subjects had sub-mucosal and intramural fibroids, respectively. Fibroids in multiple locations were seen in 17 (24.3%) women.

The median score of PBAC on starting treatment was 222.86 ± 64.59. A total of 10 (14.2%) women had dysmenorrheal along with HMB.

Effect of Mifepristone on Menstrual Bleeding

The median score of PBAC on starting treatment was 222.86 ± 64.59 (Table 1, Fig. 1). There was a statistically significant reduction in PBAC score after 1 month to 24.21 and at 3 months of treatment to 14.13 ($p < 0.0001$). A total of 49 (70%) women had amenorrhea after 1 month of starting the treatment. After 3 months of treatment initiation, 55 (78.5%) participants reported amenorrhea. Two patients did not report any improvement in symptoms despite regular treatment. Although for one of them, hemoglobin improved by 1 gm% and the fibroid volume reduced from 20.3 to 17.4 cm^3, she underwent myomectomy after 2 months of enrollment.

At 6 months, (3 months after stopping the treatment), median PBAC score was found to be higher to 245.32 ± 64.55 from a

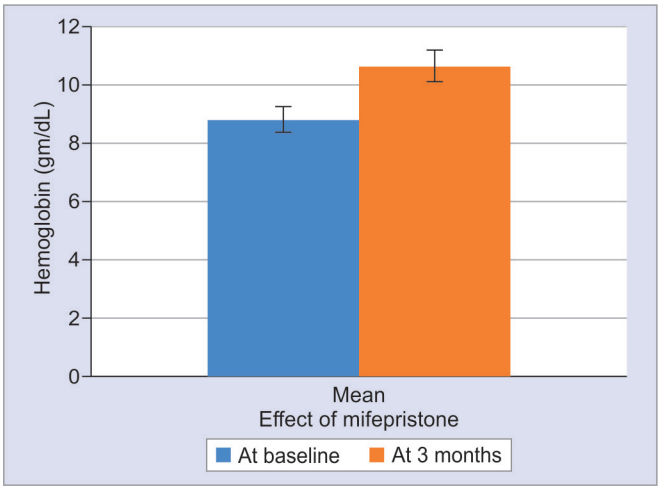

Fig. 2: Effect of mifepristone on hemoglobin

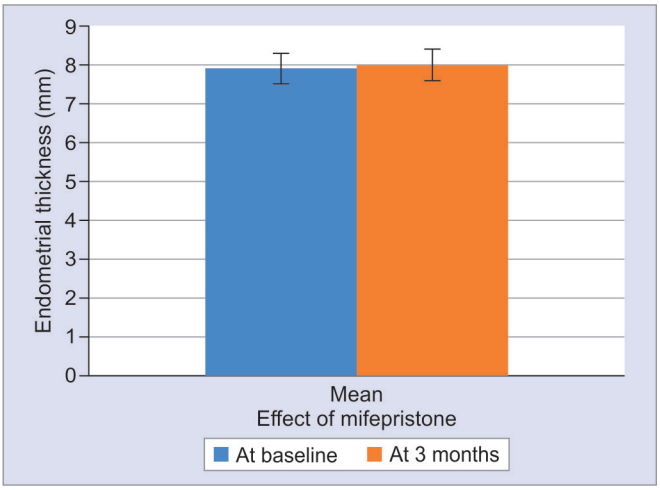

Fig. 3: Effect of mifepristone on endometrial thickness

baseline median of 222.86 ± 64.59, but not statistically significant (p-value = 0.06) (Table 1). Among those who became amenorrhea while on mifepristone, heavy menstrual flow returned in the immediate cycle after stopping the treatment in 44/70 (62.8%) study subjects. Nine (12.8%) patients had average flow (PBAC < 80) during 3 months after the treatment, but developed heavy bleeding thereafter with PBAC returning to baseline value or even more, signifying no residual effect of drug.

Effect of Mifepristone on Hemoglobin (Hb)

With mifepristone, a statistically significant improvement of 21.5% was seen in hemoglobin levels (p-value < 0.0001). After completion of 3 months therapy, the mean Hb was 10.72 ± 0.98 gm/dL as compared to the baseline Hb of 8.83 ± 1.15 gm/dL (Fig. 2).

Effect of Mifepristone on Endometrium

At the end of 3 months treatment, endometrial biopsy was performed. Endometrium was found to be secretory in 31 (44%), proliferative in 20 (29%), atrophic in 2 (3%), fragmented in 6 (9%) and hyperplasia without atypia in one (1.4%) of the study subjects. Rest of the women did not undergo biopsy as they were either unmarried or had lost to follow up. There was no significant change seen in endometrium thickness after 3 months of mifepristone (p = 0.987). The mean endometrial thickness before and at end of 3 months therapy were 7.92 ± 2.01 mm and 7.99 ± 1.3 mm, respectively (Fig. 3).

Effect of Mifepristone on the Size of Uterus and Fibroids

The mean volume of uterus decreased to 215.19 ± 129.15 cm^3 from a baseline mean of 223.12 ± 130.77 cm^3. This reduction of 3.2% was statistically significant (p = 0.046). A decrease of 2.6% was found in median fibroid volume (22.9–22.3 cm^3) after completion of treatment. The reduction in myoma volume was statistically significant (p-value = 0.005) (Fig. 4).

Side Effects of Mifepristone

Patients were followed up for any side effects at the end of 3 months mifepristone therapy. A total of 55 women (78.57%) did not report any side effects (Fig. 5). Hot flushes, anxiety, and irregular bleeding were reported by four (5.71%), one (1.43%), and one (1.43%) of the study participants, respectively. Five (7.14%) study subjects left the treatment. Mild elevation of liver enzymes (SGOT/SGPT) was found in four (5.71%) women.

Discussion

Uterine fibroids (leiomyoma or myoma), benign monoclonal tumors, are the most common benign tumors in women. Heavy or prolonged menstrual bleeding, abnormal uterine bleeding, resultant anemia, pelvic pain, infertility, and/or recurrent pregnancy loss are generally associated with uterine fibroids. Although curative treatment of this tumor relies on surgical therapies, medical treatments are considered the first-line treatment to preserve fertility and avoid or delay surgery. Fibroids cause HMB because of various reasons, increased endometrial surface, uterine volume, interference with contractility, aberrant angiogenesis and associated endometrial hyperplasia and endometrial polyp.

Mifepristone is an SPRM that causes amenorrhea and anovulation due to its antiproliferative effect on endometrium. Progesterone acting via its cognate receptors (PR-A, PR-B) plays a central role in regulation of uterine function making PR an attractive therapeutic target. The SPRM is useful in medical management of fibroids, ulipristal being FDA and DGCI approved for use. Various studies have been conducted to evaluate mifepristone in doses varying from 2.5 to 50 mg/day given for 3–6 months. Studies using doses as low as 5 mg and as high as 50 mg were found effective in reducing myoma volume by 26–57%, inducing amenorrhea in 41–100% and reducing HMB, dysmenorrhea, and pressure symptoms caused by fibroids.[3–6] A dose of 10 and 25 mg has been used in the management of fibroids, in India.[4–6] Our study was a pilot study using mifepristone 5 mg in treatment of fibroids in Indian population.

Success rate of mifepristone in reducing blood loss as measured by PBAC, was 88.57% (62/70) at 1 month and 95.38% at 3 months (62/65). A total of 3 (4.62%) patients in our study found no reduction in heavy bleeding and were considered a failure. In a study in India with 10 mg dose, no failure was reported.[4] In our study, 49 (70%) and 45 (78.5%) women developed amenorrhea after 1 and 3 months of starting the 5 mg mifepristone, respectively. It was reversible after cessation of treatment. These results were similar to that of a study in which higher dose (10 mg) mifepristone-induced reversible amenorrhea in 78% women.[7] However, another study evaluated the effect of 25 mg mifepristone and they reported amenorrhea in only

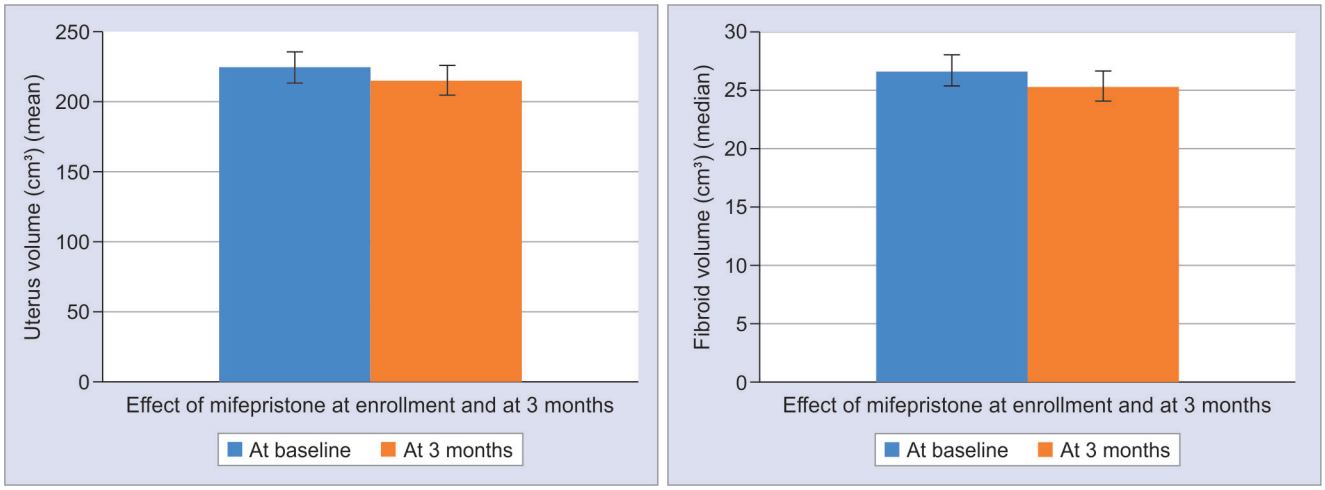

Fig. 4: Effect of mifepristone on fibroid and uterus volume

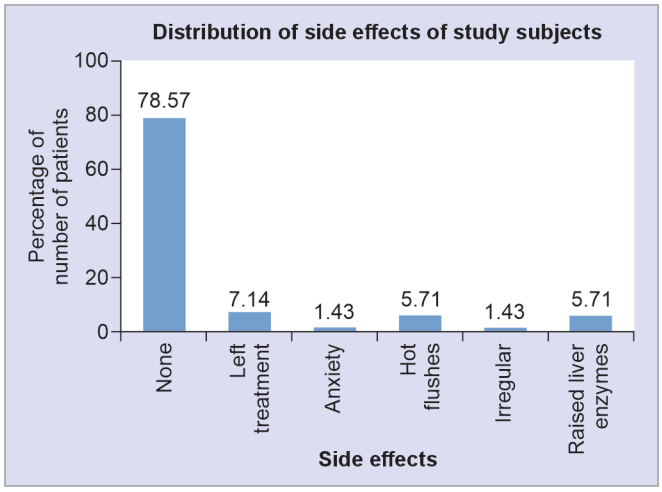

Fig. 5: Side effects of mifepristone during treatment

8% and reduced menstrual flow in 84% of women.[8] A randomized clinical trial comparing two doses of mifepristone found 10 mg mifepristone to be as effective as 25 mg in relieving menorrhagia, pain and other myoma-related symptoms.[5] Another study reported that menstrual blood loss remained significantly low in 87% women for until 6 months after initiation of therapy.[8]

At 3 months of 5 mg mifepristone, a significant improvement of 1.9 gm/dL (21.6%) in hemoglobin levels. This rise was similar to that reported with 10 mg mifepristone and greater than with 25 mg mifepristone.[7,8] This could be explained by greater proportion of patients developing amenorrhea in our study. The 5 mg dose mifepristone in our study resulted in highly significant reductions in fibroid volume ($p = 0.005$) and significant decrease in uterus volume ($p = 0.04$). Reduction in uterine size and fibroid volume has been reported by other studies using higher doses. The 25 mg dose resulted in significantly greater reduction in overall myoma size as compared to 10 mg dose.[8] However, another study using a lower dose of 12.5 mg found it to be more effective in reducing volume of leiomyoma than 25 mg dose.[6]

In our study, no significant change was seen in endometrium thickness after 3 months of mifepristone ($p = 0.987$) and endometrial histology at the end of therapy did not reveal any atypical hyperplasia or malignant changes. Previous studies with low-dose mifepristone have raised a concern of endometrial hyperplasia. Significant endometrial hyperplasia has been seen with 10 mg mifepristone for 6 months.[9] Despite paucity of mitoses, progesterone receptor modulator-associated endometrial changes (PAEC) may be mistaken for endometrial hyperplasia. The PAEC consist of cystic glandular dilatation with no evidence of atypical hyperplasia and are absolutely benign.[6]

A total of 56 out of 67 (78.5%), of study subjects, tolerated the drug well and had no side effects of mifepristone. Headache, weight gain, and loss of libido were not seen in any of our study subjects. Renal function tests remained unaltered during entire duration of therapy. Mild elevation of liver transaminases was noted in four women. These results were comparable to those of other studies that have concluded that short-term treatment with mifepristone is well tolerated.[10,11]

The aim of any treatment is to provide minimum effective dose which is also cost effective and has minimum side effects. The other available options to low-dose low-cost mifepristone is ulipristal (UPA) and GnRH. Both of them are expensive and are associated with side effects. The cost of GnRH and ulipristal is about INR 3,300 per month. The cost of 5 mg daily mifepristone regimen is Rs 327/month which is 1/10th the cost of UPA or GnRH agonist. The GnRH agonist needs parenteral administration and is associated with hypoestrogenism leading to hot flushes, decreased libido, and osteoporosis. Use of UPA is associated with the risk of liver failure that may require liver transplantation.[12,13]

The SPRM (ulipristal and mifepristone), GnRH agonist, oral contraceptives, levonorgestrel intrauterine device, aromatase inhibitor, and GNRH antagonists are used in medical management of fibroids, however, out of these only Gnrh analogs and SPRM are seen to have reduction in fibroid size.[14] Elagolix, an oral GnRH antagonist has been recently approved by the US Food and Drug Administration (FDA) and DCGI in combination with estradiol/norethindrone acetate for the management of uterine fibroids in premenopausal women up to 24 months.[15] It is expensive and does not cause amenorrhea which is sometimes required to build up hemoglobin in anemic patients. The SERM raloxifene and tamoxifen are seen to have no alleviation of HMB, fibroid size and associated symptoms.[16] Combined hormonal and oral progestin-only contraceptives can be considered in the treatment of fibroid-associated HMB, although evidence is limited

and partly based on expert opinion.[17] Again, these products can be an option for fibroids smaller than 3 cm in size mifepristone in low dose is thus a cost effective option for uterine fibroids in causing amenorrhea, which should be explained to patient and should be acceptable to them.

The strength of our study was that it was a pilot study in India using 5 mg mifepristone. The limitation of the study was that it was short-term study. The safety profile and efficacy of mifepristone in 5 mg dose can encourage its prolonged usage which needs to be a research area in future.

Conclusion

Mifepristone in a low dose of 5 mg is a low-cost alternative in medical management of fibroids with minimal side effects.

Clinical Significance

A 5 mg dose of mifepristone is an alternative medical treatment which is economically cheaper in treatments of fibroids, which has high efficacy and minimal side effects. The treatment can be given for short term. Although in this study treatment was given for 3 months a longer duration can be given as symptoms recur on stopping 5 mg of mifepristone which had no cumulative effect.

Ethical Approval

Ethical clearance was taken from hospital institutional board, Clinical Trial was registered at CTRI No- CTRI/2021/02/031195.

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