ORIGINAL ARTICLE

Low-dose Mifepristone (25 mg) in Treatment of Uterine Myoma in Perimenopausal Women

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ABSTRACT

Objectives: To evaluate the effect of low-dose mifepristone (25 mg) on symptomatic myoma in perimenoapausal women.

Study design: Prospective observational clinical trial.

Materials and methods: Ninety-three perimenopausal women of age 35 to 50 years having symptomatic myoma were selected from gynecology outpatient department and given 25 mg mifepristone once daily continuously for 3 months. Baseline uterine size, uterine volume, myoma size, volume, their number, position, characteristics, hemoglobin and blood parameters, were taken and followed monthly for 6 months. Bleeding and pain scores were checked on monthly visits. Change in above parameters were tabulated during the first 3 months treatment phase and then next 3 months post-treatment phase for analysis.

Statistical analysis: Done by calculating mean, standard deviation, standard error and percentage distribution of variables.

Results: Menorrhagia was the commonest symptom which led patients to report to hospital. Mean uterine volume reduced to 63.69% of baseline, mean dominant myoma volume reduced to 53.62% and hemoglobin level raised to 137% after complete treatment of 3 months. Changes persisted in next 3 months post-treatment follow-up, while hysterectomy was required in 10 (12.2%) cases.

Conclusion: Three months treatment of 25 mg mifepristone effectively controls bleeding, reduces the uterine and myoma volume and thus can avoid blood transfusion and hysterectomy in a lot of symptomatic myoma cases.

Keywords: Mifepristone, Myoma, Medical treatment, Antiprogesterone.

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INTRODUCTION

Leiomyoma is the common benign tumor of uterus occurring in up to 20% of women over 30 years of age leading to menorrhagia, pain and lump in abdomen. The severity of symptoms typically depends on size, number of myomas and tumor location. They represent one of the most frequent indications of operative procedures in woman of reproductive age. Incidence of hysterectomy due to leiomyoma is 2/1000 women/year or 2,00,000/year, which represents the third of all hysterectomies in USA.[1]

Apart from hysterectomy, other treatment modes have been searched since long time which includes minimally invasive embolization of feeding arteries and medical management using gonadotropin-releasing hormone (GnRH) agonist, antiprogestogens and progesterone receptor modulators etc. Long-term GnRH agonist treatment is problematic because of high cost and significant side effects due to hypoestrogenic environment produced by it. Mifepristone is a synthetic steroid with both antiprogesterone and antiglucocorticoid activities. Mifepristone (RU - 486) reduces the number of progesterone receptors in uterine body and fibroids, thus resulting in suppression of myoma size as well as impacting their vascular supply. In the present study, we had tried the low-dose 25 mg mifepristone daily for 3 months to avoid adverse side effects. The aim of the study was to evaluate the effect of mifepristone on leiomyoma volume, uterine volume at this low dose in view of avoiding hysterectomies.

MATERIALS AND METHODS

This prospective clinical trial was done at Department of Gynecology at UP Rural Institute of Medical Sciences and Research (RIMSNR) Saifai, Etawah over a period of 2 years from July 2009 to 2011 after obtaining approval from Ethics Committee of Institute and under the financial back up from UP Council of Science and Technology, Lucknow.

Nonpregnant women of 35 to 50 years age (perimenopuasal) group, having 'symptomatic myomas' (single or multiple diagnosed by pelvic ultrasonography) who wished to conserve their uterus were selected for the study. Excessive uterine bleeding was evidenced by either profuse bleeding with flooding or clots or repetitive periods lasting for more than 8 days leading to anemia. All women gave their written informed consent prior to inclusion and accepted the follow-up protocol of the project. Each woman received the mifepristone 25 mg (prepared from available 200 mg tablet by chemical balance and filled in gelatin capsules) daily for the 3 months starting from the 3rd to 5th day of menstrual cycle from the hospital.

Exclusion criteria were very large myomas greater than 10 cm in size, history of hormonal treatment in last 2 months, history of breast cancer or other genital malignancy, adenexal mass, pregnancy, suspicion of leiomyosarcoma on sonography, severe renal or liver dysfunction or any contraindication to mifepristone itself.

Blood samples were collected for hemoglobin, blood counts, baseline liver and renal function tests, bleeding time, clotting time, along with a detailed baseline pelvic ultrasound, to know the exact size and volume of uterus, number, size, volume and location of myomas and endometrial thickness at the start of treatment. Three largest diameters (A, B and C) were measured in two planes in approximately perpendicular axis in all myomas. As most of myomas are spherical or ellipsoidal, therefore volume was calculated using formula $0.523 \times A \times B \times C$. In case of multiple myomas largest one (dominant) was used for volume calculations and follow-up. Uterine size was also measured in two different axial planes and volume calculated using formula for a cone. Sonography and hematological parameters were carried out every 4th week in follow-up visits. Women were asked to keep daily records of bleeding and symptoms as pain, pressure or any side effect during study. Symptoms were graded at every visit on a 5 point 'Likert scale' (0—no symptoms, 1—light, 2—moderate, 3—severe and 4—very severe).

After 3 months, drug mifepristone was withdrawn but cases were followed up similarly for next 3 months post-treatment phase. Data were collected, tabulated and analyzed using appropriate statistical methods.

RESULTS

Total 93 cases were enrolled over 2 years from July 2009 to 2011 from Gynecology outpatient department of UP RIMSNR, Saifai, Etawah. Mean age was 38.47 ± 4.9 years. Demographic parameters shown in Table 1. Eleven cases (12%) left treatment in between and did not reported back even after intimation.

Excessive abnormal uterine bleeding (AUB) was the commonest problem reported by 75 cases (91.46%) followed by heaviness in lower abdomen in 22 (26.83%) and pain in 18 (21.95%) for which they came to hospital. Among AUB, 54.8% was menorrhagia, 14.4% polymenorrhagia and 12.2% reported menometrorrhagia. Amount of bleeding was not exactly found correlated with size of myoma in our study. Four (4.8%) women having large myoma presented with normal cycles and one (1.2%) with amenorrhea.

Bleeding stopped within 4 to 5 days of start of mifepristone and 76 women (92.68%) had complete amenorrhea during treatment phase. Seven cases (8.5%) did not responded to drug and myoma volume continued to increase progressively which later had hysterectomy done. Symptom scores for pain showed significant change from average 'four' at start of treatment to 'two' at end of treatment. No significant changes were observed in liver enzymes or renal profile of cases.

Median number of leiomyomas at baseline sonography was two (range: 1-4) in the study. Mean uterine volume decreased to 63.69% [Standard deviation (SD) ± 22.2], while mean volume of dominant leiomyoma decreased to 53.62% (SD ± 48.5) after 3 months of complete treatment. Myoma volume decreased to a greater extent compared with uterine volume. Rate of fall in myoma volume was steep initially and flattened in later half of treatment phase (Fig. 1). Hemoglobin counts improved significantly 2.8 gm + SD 1.49, from mean 8.9 gm% at start. Endometrial thickness (ET) progressively increased during the treatment phase (Table 2). Only in two cases ET crossed the 20 mm mark, after which endometrial biopsy was done and simple endometrial hyperplasia was diagnosed. No specific side effect of the drug was noted except headache (12%) in first month.

Post-treatment follow-up could be completed only in 60 women as some stopped coming to hospital after drug was withdrawn. Menstruation was regained in mean

Table 1: Demographic parameters

S.no.	*Parameters*	*N = 82*
1.	Mean age	38.47 ± 4.9 years
2.	Median parity	4 (2 - 7)
3.	Mean BMI	24.12 kg/m^2 ± 3.81
4.	Mean height	153.2 ± 4.8 cm
5.	Caste	
	• Hindu	68
	• Muslim	13
	• Christian	1
6.	Socioeconomic strata (Kuppuswami)	
	• Class I	2
	• Class II	5
	• Class III	33
	• Class IV	42
7.	Education	
	• Illiterate	34
	• Primary	10
	• 10th stand.	29
	• Graduation	9

BMI: Body mass index; Stand: Standard

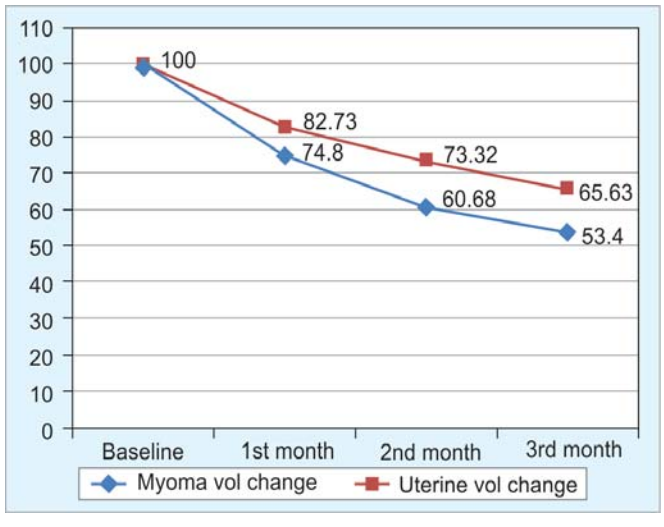

Fig. 1: Uterine and myoma volume change in treatment phase

Table 2: Clinical outcomes after mifepristone treatment

S.no.	Parameters	Volume ± SE*	Mean percentage ± SE	Change
1.	Mean baseline uterine volume (mm^3)	302124.5 ± 18245.3	100%	
	Mean uterine vol. at 1st month	249856.96	82.73 ± 14.1%	17.27% Fall
	Mean uterine vol. at 2nd month	221457.25	73.32 ± 17.6%	26.68% Fall
	Mean 3rd month end uterine volume (mm^3)	192424.7 ± 12289.2	63.69 ± 22.2%	36.31% Fall
2.	Mean baseline myoma volume (mm^3)	143957.8 ± 17669.9	100%	
	Mean myoma vol. at 1st month	107680.43	74.8 ± 36.3%	25.2% Fall
	Mean myoma vol. at 2nd month	87353.59	60.68 ± 55.9%	39.32% Fall
	Mean 3rd month end myoma volume (mm^3)	77201.9 ± 14299.3	53.4 ± 48.5%	46.38% Fall
3.	Mean baseline hemoglobin	8.9 ± 2.1 gm%	100%	
	Mean 3rd month Hb	11.82 ± 1.26	137%	Mean rise 2.8 ± 1.49 gm SD
4.	Mean baseline endomaterial thickness	76.62 mm	100%	
	Mean 3rd month end endometrial thickness	10.03 ± 2.38 mm	151.9%	51.9% Rise

*SE: Standard error; Hb: Hemoglobin; SD: Standard deviation

Table 3: Post-treatment follow-up (N = 60)

Parameters for follow-up		No. of cases	Percentage (%)
Menstruation regained	Within 1 month	22	36.6
	After 1 month	37	61.6
Bleeding	Amenorrhea persisted	1	1.6
	Normal cycles regained	32	53.33
	Heavy required tranexamic acid	27	45
Operative treatment	Polypectomy	2	3.3
	Recurrent bleeding requiring hysterectomy	4	6.6

duration of 34.72 (SD ± 17.48), days. One case persisted with amenorrhea and only four required hysterectomy for recurrence of heavy bleeding episodes (Table 3).

Incidence of hysterectomy was found to be 12.1% (10/ 82) in the study, six nonresponders to mifepristone and four for recurrence of symptoms in post-treatment phase. In two cases pedunculated submucous myoma prolapsed into vagina at 3rd and 4th month respectively, in whom polypectomy solved the problem. Blood transfusion was given in only five decompensated cases to improve their general condition.

DISCUSSION

Medical treatment that lowers estrogen levels as GnRH agonists, antagonize progesterone (mifepristone), modifies estrogen response (raloxifene), or reduces aromatase activity (letrozole) are effective in reducing the size of fibroid and improve symptoms in most of cases. Medical treatment reduces size, builds up hemoglobin and even renders surgery unnecessary, if in term the patient is going to enter menopause because fibroid being a hormone-depended tumor stops to grow after menopause.

Excessive abnormal vaginal bleeding is the most common symptom reported with myoma leading to iron deficiency anemia in women. We found that some, very small myomas also lead to significant menorrhagia. Eisinger et al[2] reported mean uterine volumes decreased by 48% after 6 months of 10 mg mifepristone and amenorrhea occurred in 61 to 65% women. Another study had reported that treatment with 5 to 10 mg of mifepristone for 1 year led to amenorrhea in 40 to 70% of cases, while treatment with 100 mg led to 100% amenorrhea.[3] Disadvantage of higher dose is antiglucocorticoid side effects. Dose of 25 mg was selected to decrease the unnecessary side effects and found satisfactory in relieving menorrhagia, pain in abdomen, improving hemoglobin and thus avoiding need for blood transfusion in our study. Mechanism of reduced bleeding and myoma size is likely to be due to structural, functional and microvascular effects of mifepristone on the endometrium and uterine musculature. In our study, response with 25 mg dose of mifepristone was found to be quiet effective in reducing uterine size to 63.69% of baseline over the period of 3 months. Others had reported 36 to 47% reduction in uterine size with very low-dose 5 to 10 mg of mifepristone.[4,10]

Engman et al[5] had shown a significant decrease ($p = 0.021$) in perceptual total leiomyoma delta volume from baseline to end of study in 50 mg mifepristone group 28% (–48 to –8) compared with 6% (–13 to +25) with placebo although total uterine volume change was not significant. Kettle et al[3] had stated 49% decline in myoma size with 100 mg mifepristone in 3 months, which is almost comparable with our results of 25 mg dose. Similar results are reported by Murphy et al.[6] A comparative study of 5, 25 and 50 mg drug suggests that most effective dose to cause clinically significant decrease in leiomyoma appears to be 25 mg daily.[7]

System review of past studies had shown endometrial hyperplasia as the notable adverse effect of the drug mifepristone.[8] Long-term use of high dose of antiprogesterone may promote an unopposed estrogen milieu leading to endometrial hyperplasia.[9]

This short-term treatment is well-tolerated, although large long-term studies are needed to add safety information, about endometrial and breast proliferation and follow-up after stopping treatment. In a reproductive age female medical therapy results may not be as good, as myoma may regrow after discontinuation of treatment. Typically, best candidates are perimenopuasal women with anemia and those who want to avoid surgery. It can be given preoperative cases to reduce size and build up hemoglobin level.

CONCLUSION

Most important and useful effect of mifepristone found to be the control of bleeding leading to improvement in hemoglobin levels and general condition. Study supports that 25 mg mifepristone daily for 3 months is effective in alleviating hysterectomy in 87.8% cases and even for presurgical management of myoma-related bleeding by inducing amenorrhea, increasing hemoglobin and reducing myoma volume.

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