ORIGINAL RESEARCH

Study the effect of long term low dose mifepristone for the treatment of fibroids in a tertiary set-up

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ABSTRACT
Background: Uterine fibroids are non-cancerous growths that form in the uterus. This tumor is the most prevalent in the uterus and female pelvis. The present study was conducted to assess the effect of long- term low dose mifepristone for the treatment of fibroids. **Materials & Methods:** 76 women diagnosed with uterine fibroids were prescribed 50 milligrams of mifepristone given per week. Patients were evaluated at 1 and 6 months. **Results:** Common symptoms were backache in 24, pelvic pain in 69, menorrhagia in 65, dysmenorrhea in 62, infertility in 12 and urinary complaints in 7 patients. The difference was non- significant (P> 0.05). The mean fibroid volume at baseline was 210 cm3, at 6 months was 106 cm3 and at 9 months was 95 cm3. The mean hemoglobin at baseline was 9.2 g/dl, at 6 months was 10.4 g/dl and at 9 months was 10.8 g/dl. There was significant reduction (P< 0.05) in fibroid volume and increase in hemoglobin after the treatment at follow ups. At baseline endometrium was normal in 71 and at 6 months was in 45. It was atrophic in 5 and 1, disordered proliferative in 0 and 2 and simple hyperplasia without atypia in 0 and 28 at baseline and at 6 months respectively. The difference was significant (P< 0.05). **Conclusion:** Therapy using 50 mg of mifepristone on a weekly basis for six months is effective and tolerable for treating symptomatic leiomyoma.
Keywords: Mifepristone, Infertility, Uterine fibroids

INTRODUCTION

Uterine fibroids, known by various names including fibroid tumors, fibromyomas, myofibroma, leiomyofibroma, fibroleiomyoma, myoma, fibroma, and leiomyoma, are non-cancerous growths that form in the uterus.[1] This tumor is the most prevalent in the uterus and female pelvis. While the incidence is generally reported to be 20–25 percent, studies employing histologic and sonographic examinations have demonstrated it can reach as high as 70–80 percent.[2] The majority of fibroids do not present symptoms; when they do show symptoms, however, patients exhibit menstrual irregularities, infertility, abdominal masses, or pressure effects. Fibroids can be managed either surgically or medically. Among the surgical options, hysterectomy is viewed as the definitive management of symptomatic uterine fibroids.[3]

For patients who wish to retain their uterus, for younger patients, and for those who want to have children, myomectomy is an option. For patients for whom surgery is not advisable, and to lessen symptoms and indications, medical management can be provided.[4] The drugs available are antifibrinolytics such as tranexamic acid,

danazol, GnRH analogs, progestogens, and the antiprogesterone mifepristone. The FDA approved mifepristone, an antiprogesterone drug marketed under the trade name "Mifegyne," as an abortifacient on September 28, 2000.[5] This drug significantly reduced the immune reactivity of progesterone receptors in myoma and myometrial tissue, suggesting that these tumors may regress due to a direct antiprogesterone effect.[6] Although a consensus recommends a daily dose of 10 to 20 mg for fibroid treatment, various dosage regimens have been proposed. There has been no indication that higher doses lead to a greater beneficial effect, but it has been noted that the side effects increase.[7]

AIM AND OBJECTIVES

The present study was conducted to assess the effect of long- term low dose mifepristone for the treatment of fibroids.

MATERIALS AND METHODS

Study Design

- Type: Prospective interventional cohort study.
- Objective: To evaluate the effectiveness and safety of long-term, low-dose mifepristone in women with uterine fibroids.
- Duration: 9 months (6 months of treatment + 3 months post-treatment follow-up).

Study Population

- Total Participants: 76 women.
- Demographics: Women diagnosed with uterine fibroids.
- Consent: Written informed consent was obtained from all participants.

Study Place

- The study was conducted in the Department of Obstetrics and Gynecology, Nalanda Medical College and Hospital, Patna, Bihar, India.

Study Duration

- The study was carried out over a period of 18 months, from June 2016 to November 2018, allowing for recruitment, examination, and analysis.

Study Duration

- Total Duration: 9 months per participant.
  - Treatment Phase: 6 months.
  - Follow-up Phase: 3 months post-treatment.

Inclusion Criteria

- Women diagnosed with uterine fibroids confirmed via transvaginal sonography.
- Women of reproductive age.
- Women who gave written informed consent.
- Women with regular menstrual cycles before starting treatment.

Exclusion Criteria

- Women with suspected or confirmed malignancy.
- Known liver disease or abnormal liver function at baseline.
- Women with endometrial hyperplasia.
- Those on hormonal therapy or any contraindications to mifepristone.
- Pregnant or breastfeeding women.
- Women with co-morbid systemic diseases.

Ethical Considerations

- Written informed consent was taken from all participants.
- The study ensured the ethical treatment of subjects in compliance with the Declaration of Helsinki.
- Ethical committee approval (although not mentioned, it is standard practice and should be included).

Study Procedure

- Baseline Evaluation:
  - Detailed history including name, age, menstrual history.
  - Blood investigations: CBC, Liver Function Tests (LFT), Renal Function Tests (RFT), Thyroid Function Tests.
  - Premenstrual endometrial biopsy to rule out endometrial hyperplasia.
  - Transvaginal sonography (TVS) to measure fibroid volume.
  - Menstrual blood loss evaluated using Pictorial Blood Assessment Chart (PBAC).
- Treatment:
  - Oral Mifepristone 50 mg once per week for 6 months.
- Monitoring & Follow-up:
  - Evaluation at 1 and 6 months during treatment.
  - Follow-up period of 3 months after stopping medication:
    - Changes in menstrual pattern.
    - Fibroid volume measurement via TVS.
    - Haemoglobin levels.
    - Liver function tests.
    - Repeat endometrial biopsy at 6 months post-treatment.

Outcome Measures

- Primary Outcomes:
  - Change in fibroid volume (measured via transvaginal sonography).
  - Menstrual blood loss (PBAC score).

- Haemoglobin level.
- Secondary Outcomes:
  - Liver function status.
  - Menstrual pattern changes post-treatment.
  - Histological changes in endometrial biopsy.

Statistical Analysis

- Data were compiled and statistically analyzed using appropriate software (SPSS 20.0.).
- Descriptive statistics used for baseline characteristics.
- Comparative analysis of pre- and post-treatment parameters.
- P value < 0.05 was considered statistically significant.
- Tests such as paired t-test or Wilcoxon signed-rank test (depending on data distribution) may have been used.

RESULTS

Table 1: Assessment of Symptoms

Symptoms	Number	P value
Backache	24	0.18
Pelvic pain	69	
Menorrhagia	65	
Dysmenorrhea	62	
Infertility	12	
Urinary complaints	7	

Table 1 shows that common symptoms were backache in 24, pelvic pain in 69, menorrhagia in 65, dysmenorrhea in 62, infertility in 12 and urinary complaints in 7 patients. The difference was non-significant (P> 0.05).

Table 2: Assessment of Parameters

Parameters	Variables	Number	P value
Fibroid volume (cm^3)	Baseline	210	0.01
	6 months	106	
	9 months	95	
Hemoglobin (g/dl)	Baseline	9.2	0.05
	6 months	10.4	
	9 months	10.8	

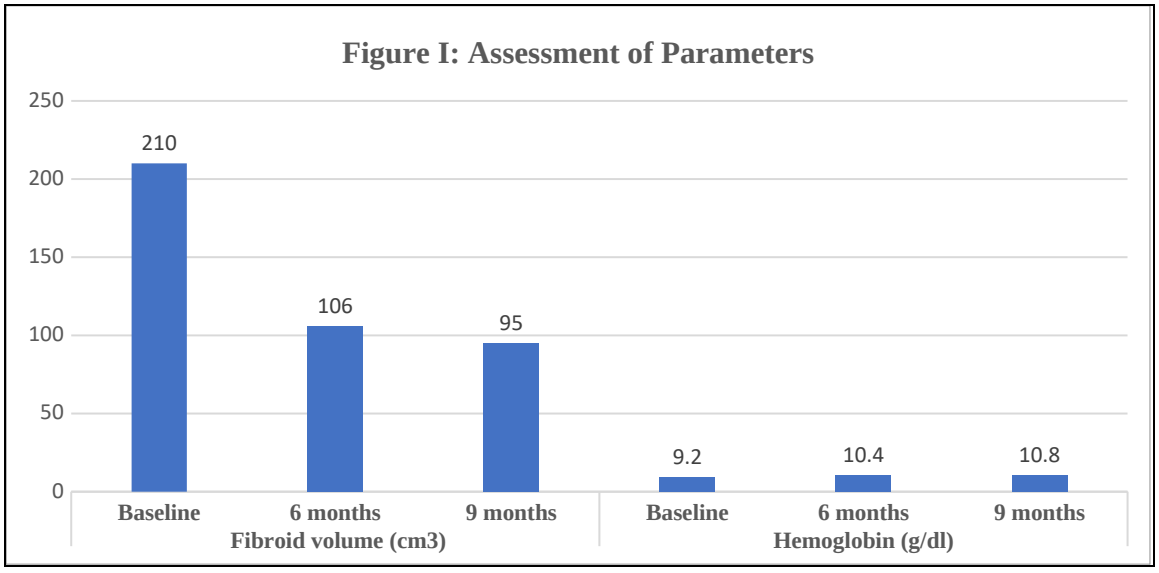

Table 2, figure I shows that mean fibroid volume at baseline was 210 cm3, at 6 months was 106 cm3 and at 9 months was 95 cm3. The mean hemoglobin at baseline was 9.2 g/dl, at 6 months was 10.4 g/dl and at 9 months was 10.8 g/dl. There was significant reduction (P< 0.05) in fibroid volume and increase in hemoglobin after the treatment at follow ups.

Table 3: Evaluation of Effect on Endometrium

Endometrium	Baseline	At 6 months	P value
Normal	71	45	0.01
Atrophic	5	1	
Disordered proliferative	0	2	
Simple hyperplasia without atypia	0	28	

Table 3 shows that at baseline endometrium was normal in 71 and at 6 months was in 45. It was atrophic in 5 and 1, disordered proliferative in 0 and 2 and simple hyperplasia without atypia in 0 and 28 at baseline and at 6 months respectively. The difference was significant (P< 0.05).

DISCUSSION

It has been demonstrated by numerous expert panels that the histological changes resulting from the ongoing use of low-dose mifepristone are not merely hyperplasias, as was previously thought, but rather "progesterone-associated endometrial changes" (PAECs).[8] PAECs are marked by a number of histological characteristics, such as cyst-like dilations in the endometrial glands with occasional secretions, abnormal blood vessels, and alterations in the relationship between glandular and connective tissue.[9] The present study was conducted to assess the effect of long- term low dose mifepristone for the treatment of fibroids.

We found that common symptoms were backache in 24, pelvic pain in 69, menorrhagia in 65, dysmenorrhea in 62, infertility in 12 and urinary complaints in 7 patients. In a study by Kapur A et al[10], majority of the study population comprised of perimenopausal women, i.e., 41–45 years (44 %). Fifty percent of the patients were Para 2 and belonged to the perimenopausal age-group (18 out of 36). The dominant presenting symptom was menorrhagia associated with dysmenorrhea and pelvic pain. After 6 months of treatment with mifepristone, 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 %). Immediate reduction in bleeding PV was observed in 100 %, and 88.89 % (32/36) patients attained amenorrhea. The mean hemoglobin increased from 9.18 to 10.82 g/dl (p = 0.001). There was a transient rise in mean transaminases (AST/ALT) levels at 6 months which reverted to normal at 9 months follow-up.

We found that mean fibroid volume at baseline was 210 cm3, at 6 months was 106 cm3 and at 9 months was 95 cm3. The mean hemoglobin at baseline was 9.2 g/dl, at 6 months was 10.4 g/dl and at 9 months was 10.8 g/dl. There was significant reduction (P< 0.05) in fibroid volume and increase in hemoglobin after the treatment at follow ups. Bagaria M et al[11] evaluated the effect of low-dose mifepristone on leiomyoma-related symptoms, uterine and leiomyoma in women with symptomatic leiomyomata. 40 patients with symptomatic leiomyoma and normal endometrial histology were randomised to receive 10 mg mifepristone (group 1) or placebo (group 2) daily for three months. Significant change was noticed between the two groups for mean menstrual blood loss (MBL) by first month. Menstrual blood loss declined by 94.8% in group 1 at three months and 84.2% patients attained amenorrhoea in this group. In group 1 complete relief of dysmenorrhoea occurred in significant number of women (80%) but only 33% patients got rid of pelvic pain. There was no change in these symptoms in group 1 Backache, urinary complaints and dyspareunia were not relieved in either group. Uterine, leiomyoma and largest leiomyoma volume declined by 26-32% in group 1 as compared to none in group 2, and this difference was statistically significant only by the end of the third month of therapy. Mean haemoglobin increased from 9.5 to 11.2 g/dL in group 1. In group 1, at the end of therapy, 63.1% of patients had endometrial hyperplasia without atypia.

We found that at baseline endometrium was normal in 71 and at 6 months was in 45. It was atrophic in 5 and 1, disordered proliferative in 0 and 2 and simple hyperplasia without atypia in 0 and 28 at baseline and at 6 months respectively. Carbonell et al[12] evaluated the safety and improvement in quality of life using 10 mg and 5 mg daily doses of mifepristone for the treatment of uterine fibroids. Seventy subjects with symptomatic uterine fibroids took one daily capsule of 10 mg or 5 mg mifepristone orally for 9 months. There were 30/49 (61.2%) and 13/24

(54.2%) diagnoses of endometrial changes associated with mifepristone in the 10 mg and 5 mg groups, respectively (P = 0.282). At every evaluation visit the average endometrial thickness was significantly greater in the 10 mg group than in the 5 mg group (P = 0.013, P = 0.002, and P = 0.013, respectively). Only five subjects had slight elevations in their hepatic transaminases after 9 months' treatment. Sixteen of 35 (45.7%) and eight of 33 (24.2%) subjects had the occasional hot flush in the 10 mg and 5 mg groups, respectively (P = 0.032). In total, there were 12.9 ± 4.6 (n = 21) and 9.1 ± 3.9 (n = 18) days of irregular bleeding in the 10 mg and 5 mg groups, respectively (P = 0.009).

LIMITATIONS OF THE STUDY

- Sample Size: Only 76 women were included; results may not be generalizable to a larger population.
- Short Follow-up: Only 3 months of follow-up after stopping treatment, which may not fully capture long-term recurrence or adverse effects.
- Single Dose Regimen: Only one dosage (50 mg weekly) was evaluated; dose-response relationships could not be studied.
- No Control Group: Absence of a placebo or alternative treatment group limits the ability to compare efficacy objectively.
- Single-centre Study: Results may vary in different settings with different patient demographics.
- Endometrial Biopsy Timing: Only two biopsy points (pre-treatment and 6 months post-treatment); interim changes might have been missed.
- Compliance Monitoring: There is no mention of methods to ensure adherence to weekly dosing.
- No Quality-of-Life Measures: Subjective patient-reported outcomes (e.g., pain, satisfaction) were not assessed.

CONCLUSION

Authors found that therapy using 50 mg of mifepristone on a weekly basis for six months is effective and tolerable for treating symptomatic leiomyoma.

REFERENCES

1. Fiscella K, Eisinger SH, Meldrum S, Feng C, Fisher SG, Guzick DS. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstet Gynecol. 2006;108(6):1381–1387.
2. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell-Danielsson K. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo- controlled trial. Hum Reprod. 2009;24(8):1870–1879.
3. Yang Y, Zheng S, Li K, et al. Treatment of uterine leiomyoma by two different doses of mifepristone. Zhonghua Fu Chan Ke Za Zhi. 1996;31(10):624–626.
4. Baird DT, Brown A, Critchley HO, Williams AR, Lin S, Cheng L. Effect of long-term treatment with low-dose mifepristone on the endometrium. Hum Reprod. 2003;18(1):61–68.
5. Spies JB, Warren EH, Mathias SD, Walsh SM, Roth AR, Pentecost MJ. Uterine fibroid embolization: measurement of health-related quality of life before and after therapy. J Vasc Interv Radiol. 1999;10(10):1293–1303.
6. Brown A, Cheng L, Lin S, Baird DT. Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. J Clin Endocrinol Metab. 2002;87(1):63–70.
7. Breech LL, Rock JA. Leiomyomata uteri and myomectomy. In: Rock JA, Jones HW III, editors. Te Linde's operative gynecology. 10. New Delhi: Wolters Kluwer Pvt Ltd; 2010. pp. 687–726.
8. Buttram VC, Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril. 1981;36:433–445.
9. Kulshrestha V, Kriplani L, Agarwal N, et al. Low dose Mifepristone in medical management of uterine leiomyoma—an experience from a tertiary care hospital from north India. Indian J Med Res. 2013;137:1154–1162.
10. Kapur A, Angomchanu R, Dey M. Efficacy of use of long-term, low-dose mifepristone for the treatment of fibroids. The Journal of Obstetrics and Gynecology of India. 2016 Oct;66:494-8.
11. Bagaria M, Suneja A, Vaid NB, et al. Low-dose Mifepristone in treatment of uterine leiomyoma: a randomized double-blind placebo-controlled clinical trial. Aust N Z J Obstet Gynaecol. 2009;49:77–83.
12. Carbonell JL, Acosta R, Perez Y, et al. Safety of 10 mg versus 5 mg of Mifepristone during 9 months for the treatment of uterine fibroids. Double-blind randomized clinical trial. Int J Women's Health. 2013;5:115–124.